Endocrine Complications of Cancer Therapy

5

Susan R. Rose, Sarah Lawson,
Karen Burns, and Thomas E. Merchant

Contents

S.R. Rose, MD (✉) • S. Lawson
Division of Endocrinology and Metabolism, Cincinnati Children's Hospital Medical Center and University of Cincinnati, 3333 Burnet Avenue, MLC 7012, Cincinnati, OH 45229, USA
e-mail: susan.rose@cchmc.org; sarah.lawson@cchmc.org

K. Burns
Division of Hematology and Oncology, Cincinnati Children's Hospital Medical Center and University of Cincinnati, 3333 Burnet Avenue, MLC 7012, Cincinnati, OH 45229, USA
e-mail: Karen.burns@cchmc.org

T.E. Merchant
Division of Radiation Oncology, St Jude Children's Research Hospital, Memphis, TN, USA
e-mail: Thomas.merchant@STJUDE.ORG

C.L. Schwartz et al. (eds.), *Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach*, Pediatric Oncology, DOI 10.1007/978-3-319-16435-9_5

Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
AM	Morning
AMH	Anti-Mullerian hormone
BMD	Bone mineral density
BMI	Body mass index
CNS	Central nervous system
CT	Computed tomography
DXA	Dual-energy x-ray absorptiometry
FSH	Follicular-stimulating hormone
GH	Growth hormone
GHD	GH deficiency
GHRH	GH-releasing hormone
GnRH	Gonadotropin-releasing hormone
Gy	Gray
HPA	Hypothalamic-pituitary axis
IGFBP3	Insulin-like growth factor binding protein
IGF-I	Insulin-like growth factor
LH	Luteinizing hormone
MR	Magnetic resonance
OGTT	Oral glucose tolerance test
PM	Afternoon
PRL	Prolactin
RT	Radiation therapy
SD	Standard deviation
T3	Triiodothyronine
T4	Thyroxine
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone

5.1 Introduction

Endocrinopathy after therapeutic irradiation represents a treatable late effect of successful cancer therapy and highlights the importance of careful follow-up for adults and children. The endocrine effects of irradiation have been extensively studied and demonstrate the systemic manifestations of late effects after localized or large volume irradiation, the differential sensitivity of functional subunits of the hypothalamus and other critical endocrine organs to radiation dose, the low-dose radiation effects in normal tissues, and the benefit of newer radiation methods and modalities.

There is significant morbidity and mortality linked to the late effects of cancer therapy [67]. Despite our understanding of the endocrine effects of cancer therapy, this information is often not considered when models of treatment outcomes and therapy effects are developed. It is possible that the contribution of endocrine deficits to morbidity and mortality is not fully appreciated. Endocrine deficiencies affect patients who do not have pituitary tumors [1] as well as those whose treatment volume encompasses the hypothalamic-pituitary axis. Rare late effects of treatment most often attributed to the volume of irradiation might be linked to the indirect effects of damage to the hypothalamic-pituitary axis or other organs of the endocrine system. A striking example is the link between anticancer therapy for patients with pituitary tumors and craniopharyngioma. These patients are at increased risk for mortality mainly due to radiation-associated vascular disease rather than endocrinologic abnormalities [68]. There needs to be increased recognition of endocrine sequelae of cancer therapy, the contribution of radiation therapy, and an emphasis on early detection and follow-up because of the potential impact on quality of life [72]. Long-term survivors are at increased risk for broad-ranging side effects including metabolic syndrome, growth hormone deficiency, and cardiovascular disease [27]. The field of endocrinology is uniquely capable of intervention to treat the late effects of cancer therapy. Endocrinologists should be consulted early in the management of patients at high risk for preexisting endocrine deficiencies and those likely to develop these common complications.

5.2 Pathophysiology

5.2.1 Normal Hypothalamic-Pituitary Axis

The hypothalamic-pituitary axis (HPA) is the primary interface between the nervous system and the endocrine system. The actions and interactions of the endocrine and nervous systems constitute the major regulatory mechanisms for virtually all physiologic activities. The hypothalamus has extensive neural communications with

other brain regions and regulates brain functions including temperature, appetite, thirst, sexual behavior, and fear. The hypothalamus also contains two types of neurosecretory cells (Fig. 5.1): (1) neurohypophysial neurons, which transverse the hypothalamic-pituitary stalk and release vasopressin and oxytocin from their nerve endings in the posterior pituitary, and (2) hypophysiotropic neurons, which secrete releasing hormones into portal hypophyseal vessels. The releasing hormones regulate secretion of hormones from the anterior pituitary (Table 5.1).

5.2.1.1 Growth Hormone

Growth hormone (GH) is a 191-amino-acid polypeptide hormone synthesized and secreted by the somatotrophs in the anterior pituitary gland in response to hypothalamic releasing hormones, primarily GH-releasing hormone (GHRH). In addition, ghrelin secretion from the stomach during fasting also contributes to GH secretion [51]. GHRH levels are usually steady, while somatostatin secretion is interrupted intermittently. Somatostatin inhibits GH release but paradoxically contributes to synthesis of GH in the pituitary [12]. When somatostatin concentrations decrease, the tonic concentration of GHRH causes release of GH into the systemic circulation. Factors such as neuropeptide Y, leptin, galanin, and ghrelin also affect GH secretion. In healthy children and adults, GH secretion is pulsatile, particularly during sleep, with two to six pulses per night [61]. In adolescents, additional pulses occur during the day, and the pulses have higher peaks than those seen in children and adults (Fig. 5.2a).

Circulating serum GH stimulates production of insulin-like growth factor I (IGF-I) in all tissues. IGF-I mediates GH effects on growth, bone mineralization, and body composition (decreased truncal fat deposition, increased lean muscle mass) [78]. IGF-I is bound to IGF-binding proteins such as IGFBP3 and is transported in the blood. IGF-I and IGFBP3 concentrations are stable during the day, and each reflects the integrated concentration of secreted GH.

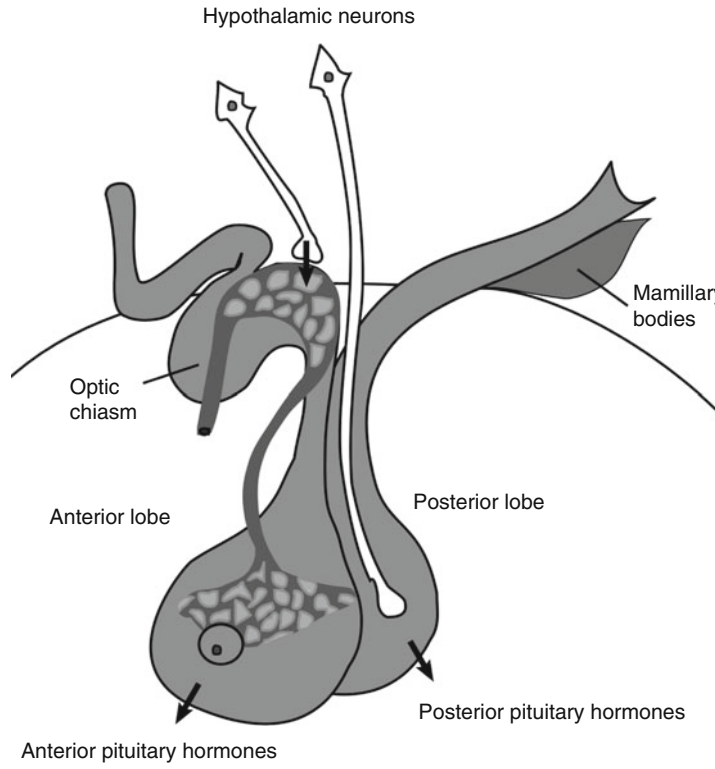

Fig. 5.1 Diagrammatic representation of the hypothalamic-pituitary axis

Table 5.1 Anterior pituitary hormones and major hypothalamic regulatory factors

Pituitary hormone	Hypothalamic factor	Effect
Growth hormone	Growth hormone-releasing hormone	+
	Somatostatin	–
Prolactin	Dopamine	–
Luteinizing hormone	Gonadotropin-releasing hormone	+
Follicle-stimulating hormone	Gonadotropin-releasing hormone	+
Thyroid-stimulating hormone	Thyroid-releasing hormone	+
	Somatostatin	–
Adrenocorticotropin	Corticotropin-releasing hormone	+
	Vasopressin	+

Effects on the hypothalamus were either stimulatory (+) or inhibitory (–)

5.2.1.2 Gonadotropins

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are glycoprotein hormones both stored in the same cells in the anterior pituitary. Their overall patterns of secretion vary according to the age and gender of the person. The pituitary gland produces and secretes LH and FSH in a pulsatile manner in response to episodic release of GnRH from the hypothalamus (Fig. 5.2a). The hypothalamic stimulus is actively inhibited between 6 months of age and the usual age of onset of puberty (Fig. 5.2b). This inhibition can be disturbed by tumor mass, cranial surgery, or irradiation, thereby resulting in precocious puberty in children. In men, LH stimulates testosterone production in Leydig cells of the testes; normal spermatogenesis requires both LH and FSH. In women, FSH stimulates production of estrogen and LH stimulates production of progesterone in the ovary. The LH surge near the end of the follicular phase of the menstrual cycle is necessary to stimulate ovulation. Development of the ovarian follicles is largely under FSH control, and secretion of estrogen from follicles is dependent on both FSH and LH.

5.2.1.3 Thyroid-Stimulating Hormone

Thyrotropin, or thyroid-stimulating hormone (TSH), is a glycoprotein hormone synthesized in the anterior pituitary. Secretion of TSH is stimulated by TSH-releasing hormone (TRH) and inhibited by somatostatin and dopamine secreted from the hypothalamus. In persons older than 12 months of age, there is a circadian pattern to TSH release. TSH concentration is low after 1000 h and in the afternoon, rises dramatically (*surges*) after 1900 h, and reaches highest concentrations between 2200 and 0400 h (Fig. 5.2a) [58]. Thus, at least one third of the trophic influence of TSH on the thyroid gland occurs at night. TRH is necessary for TSH synthesis, posttranslational glycosylation, and secretion of a fully bioactive TSH molecule from the pituitary. Altered TSH glycosylation, resulting in altered bioactivity, is seen in mixed hypothyroidism (central hypothyroidism with mild TSH elevation [5–15 mU/L]) [34, 56].

TSH stimulates the thyroid gland to produce thyroxine (T4) and triiodothyronine (T3). T4 and T3 circulate in the blood stream bound to thyroxine-binding globulin and albumin; only small amounts are free or unbound. Free T4 undergoes intracellular deiodination to form free T3, which interacts with DNA in the cell nucleus to influence cellular mRNA and protein synthesis. Free T4 provides negative feedback at the hypothalamus and pituitary to modulate the secretion of TRH and TSH.

5.2.1.4 Adrenocorticotropin

Adrenocorticotropin (ACTH) is a 39-amino-acid peptide hormone processed in the corticotrophs from a large precursor molecule, pro-opiomelanocortin. In healthy individuals, hypothalamic corticotrophin-releasing hormone and vasopressin released in two or three synchronous pulses per hour synergistically stimulate secretion of ACTH from the pituitary [14]. ACTH secretion is pulsatile and varies throughout the day; it peaks before the person awakens in the morning (Fig. 5.2a), increases with stress, and is inhibited by glucocorticoid medications. Since cortisol secretion is regulated by ACTH, the pattern of cortisol secretion is similar to that of secretion of ACTH. In addition to the negative feedback of glucocorticoids, ACTH inhibits its own secretion (short-loop feedback).

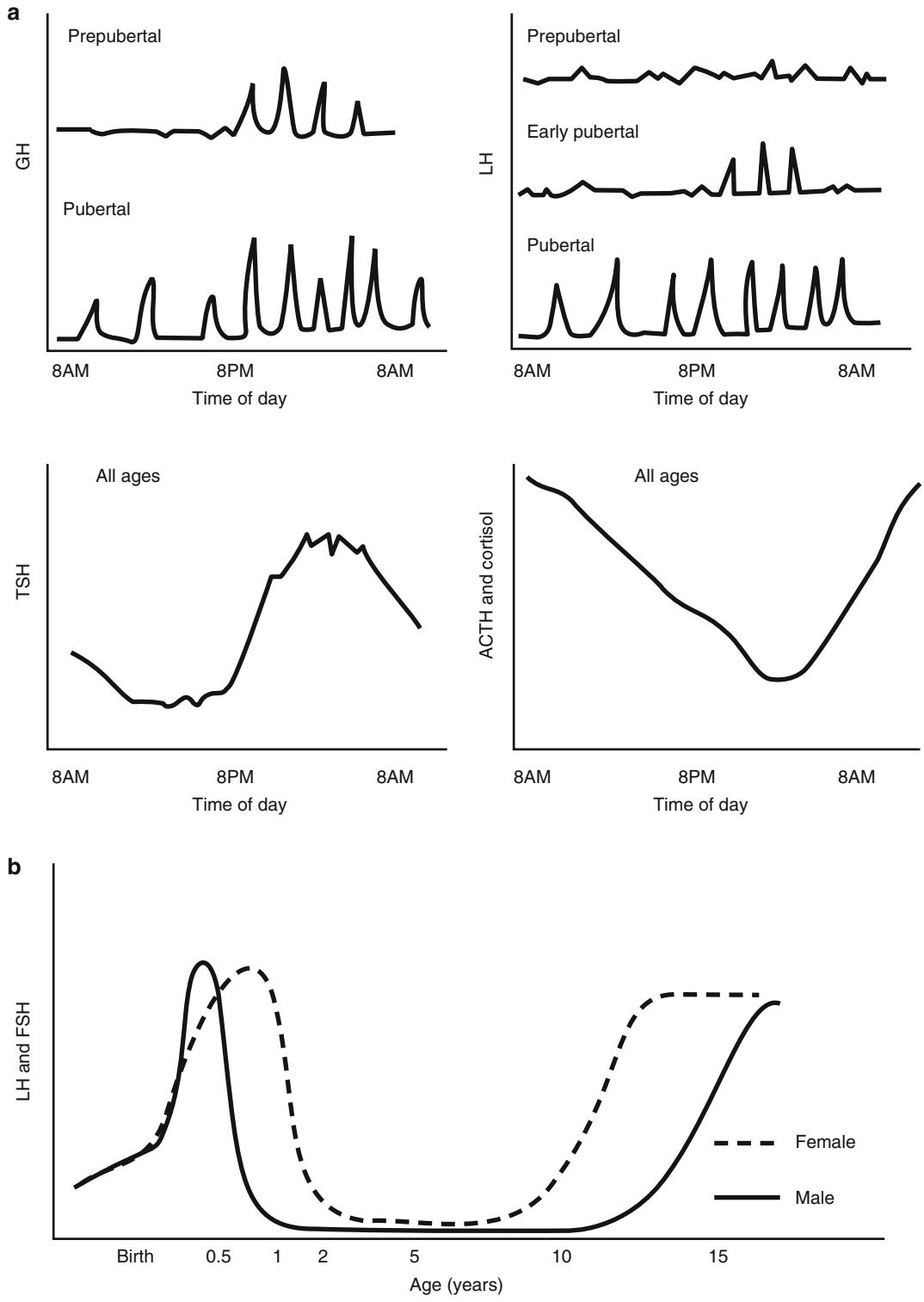

Fig. 5.2 Typical daily pattern of hormone secretion and changes with pubertal status and time of day in normal individuals (**a**) growth hormone (*GH*), luteinizing hormone (*LH*), thyroid-stimulating hormone (*TSH*), and adrenocorticotropin (*ACTH*) and cortisol secretion. (**b**) Normal changes in LH and FSH levels from infancy to adolescence

5.2.1.5 Prolactin

Prolactin (PRL) is a 198-amino-acid polypeptide hormone synthesized and secreted from lactotrophs of the anterior pituitary. A precursor molecule is also secreted and can constitute as much as 10–20 % of the PRL immunoreactivity in the plasma of healthy persons. Hypothalamic control of PRL secretion (primarily through dopamine release) is different than that of the other pituitary hormones in that the hypothalamus inhibits secretion of PRL rather than stimulating it. Thus, elevated PRL levels can be a useful marker of hypothalamic disorders that leave the pituitary intact.

5.2.1.6 Antidiuretic Hormone

Antidiuretic hormone (ADH) or vasopressin is a peptide hormone synthesized in the hypothalamic neurohypophyseal neurons, transported through the pituitary stalk in long axons, and released from the nerve terminals in the posterior pituitary. ADH is secreted in response to reduced plasma volume and increased plasma osmolality. In normal individuals, ADH secretion is increased when there is no fluid intake, such as during sleep or in dehydration.

5.2.2 Injury of the Hypothalamic-Pituitary Axis in Patients with Cancer

The hypothalamic-pituitary axis (HPA) is vulnerable to damage by certain tumors, surgical trauma, irradiation, chemotherapy, and other common risk factors (Table 5.2) [18, 57]. Patients with tumors in the area of the HPA (e.g., craniopharyngioma or hypothalamic/chiasmatic tumor) are at particular risk for neuroendocrinopathy [23, 42]. Many HPA injuries are attributable to damage caused by radiation therapy (RT) [57]. However, the occurrence of pre-RT neuroendocrinopathies in pediatric patients with brain tumors is high. Of 68 pediatric patients in one study [44], 45 (66 %) showed evidence of neuroendocrinopathy before RT, including 15 of 32 patients with tumors in the posterior fossa not adjacent to the HPA. Seventeen of the 45 patients (38 %) had abnormality in GH, 19 (43 %) in TSH, 10 (22 %) in ACTH, and 6 (13 %) in gonadotropin. In addition, patients who receive chemotherapy alone [with no history of RT or central nervous system (CNS) tumor] may also be at risk for neuroendocrinopathy. Of 31 such patients referred after chemotherapy for evaluation of altered growth and development, 48 % had GH deficiency, 52 % had central hypothyroidism, and 32 % had pubertal abnormalities [62].

GH deficiency is often the first hypothalamic-pituitary deficiency to emerge after injury to the HPA, followed by deficiencies of gonadotropin, TSH, and ACTH [18, 70]; however, these deficiencies can develop in any order [44, 59, 71]. Although the most common neuroendocrinologic abnormality in survivors of childhood cancer is GH deficiency (see Sect. 5.3.1), hypothyroidism is at least as prevalent when sensitive testing methods are used (see Sect. 5.3.4) [59]. The next most common alterations are in pubertal timing (early, rapid, precocious, delayed, or absent) (see Sects. 5.3.2 and 5.3.3). ACTH deficiency, though less common than the other disorders, has more serious consequences if it is not detected (see Sect. 5.3.5). Diabetes insipidus rarely develops after chemotherapy or irradiation, but commonly occurs after surgery in the hypothalamic-pituitary area or in association with histiocytosis or germinoma (see Sect. 5.3.7). Hypothalamic injury resulting from tumor, surgery, or irradiation can result in unrelenting weight gain, termed hypothalamic obesity (see Sect. 5.3.9). Finally, osteopenia may result from hypothalamic-pituitary deficiency, particularly GH deficiency, hypothyroidism, and hypogonadism (see Sect. 5.3.8).

5.2.3 Contribution of Radiation to Hypothalamic-Pituitary Axis Injury

Radiation therapy (RT) is a significant contributor to neuroendocrine complications observed after treatment for CNS tumors, CNS preventative therapy for leukemia, and following total

Table 5.2 Risk factors for endocrine disorders, diagnostic studies, and treatment options

Disorder	Highest risk	Diagnostic studies[a]	Treatment options[a]
GH deficiency	≥18 Gy CRT Pretransplant CRT TBI Young age Tumor near HPA Hydrocephalus	IGF-I, IGFBP-3 Bone age radiograph GH stimulation tests	Recombinant GH (SC) GnRH agonist (IM) (If pubertal maturity too advanced for height)
Gonadotropin deficiency	≥30 Gy CRT Tumor near HPA	LH, FSH, AMH, inhibin, estradiol, or testosterone (4–8 AM) Bone age GnRH stimulation test	Estrogen/progestin (O or T) (female) Testosterone (IM or T) (male)
Precocious puberty	18–24 Gy CRT Female Young age Tumor near HPA	LH, FSH, estradiol, or testosterone (4–8 AM) Bone age Pelvic ultrasound (female) ± GnRH stimulation test ± GH stimulation test	GnRH agonist (IM)
TSH deficiency	≥30 Gy CRT TBI Tumor near HPA Hydrocephalus	Free T4, TSH (8 AM) AM-PM TSH ratio Nocturnal TSH surge	L-thyroxine (O)
ACTH deficiency	≥30 Gy CRT Tumor near HPA Hydrocephalus	Cortisol (8 AM) Low-dose ACTH stimulation test	Hydrocortisone (O) Stress dosing (O, IM, or IV)
Hyperprolactinemia	≥50 Gy CRT Tumor near HPA	Prolactin	Dopamine agonists (O)
Diabetes insipidus	Histiocytosis Germinomas Tumor or tumor-related cysts near HPA	Simultaneous serum and urine osmolarity after 8–12 h without fluid intake Water deprivation test	Desmopressin (O) DDAVP (SC or IN)
Osteopenia	Low GH, TSH, or LH/FSH High prolactin Low vitamin D intake	DXA or quantitative CT 25OH-vitamin D level	Calcium + vitamin D (O) ± Bisphosphonates (O or IV)
Hypothalamic obesity	Young age (<6 years) ≥50 Gy (hypothalamus) Tumor near HPA	Fasting insulin and glucose Oral glucose tolerance test with insulin levels	Diet and exercise Ritalin or dexedrine (O) Metformin (O) (monitor for hypoglycemia) Octreotide (SC) Bariatric surgery

Abbreviations: *GH* growth hormone, *CRT* cranial radiation therapy, *TBI* total body irradiation, *HPA* hypothalamic-pituitary axis, *IGF-I* insulin-like growth factor I, *IGFBP3* IGF-binding protein 3, *GHRH* growth hormone-releasing hormone, *GnRH* gonadotropin-releasing hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *AMH* anti-Mullerian hormone, *T4* thyroxine, *TSH* thyroid-stimulating hormone, *TRH* thyrotropin-releasing hormone, *ACTH* adrenocorticotropin, O oral, *SC* subcutaneous, *IM* intramuscular, *IN* intranasal, *IV* intravenous, *T* topical

[a]See text for more details

body irradiation. Similar complications are observed when the HPA is incidentally irradiated in the treatment of nasopharyngeal cancer, retinoblastoma, Hodgkin disease with involvement of Waldeyer's ring, and pediatric sarcomas of the head and neck (e.g., parameningeal and orbital rhabdomyosarcoma) (Fig. 5.3). The incidence and time to onset of neuroendocrine sequelae after RT are difficult to predict because of other contributors to HPA dysfunction that may coincide temporally with the administration of RT. A notable example is hydrocephalus which can cause mass effect in the region of the anterior third ventricle and generalized diminished blood

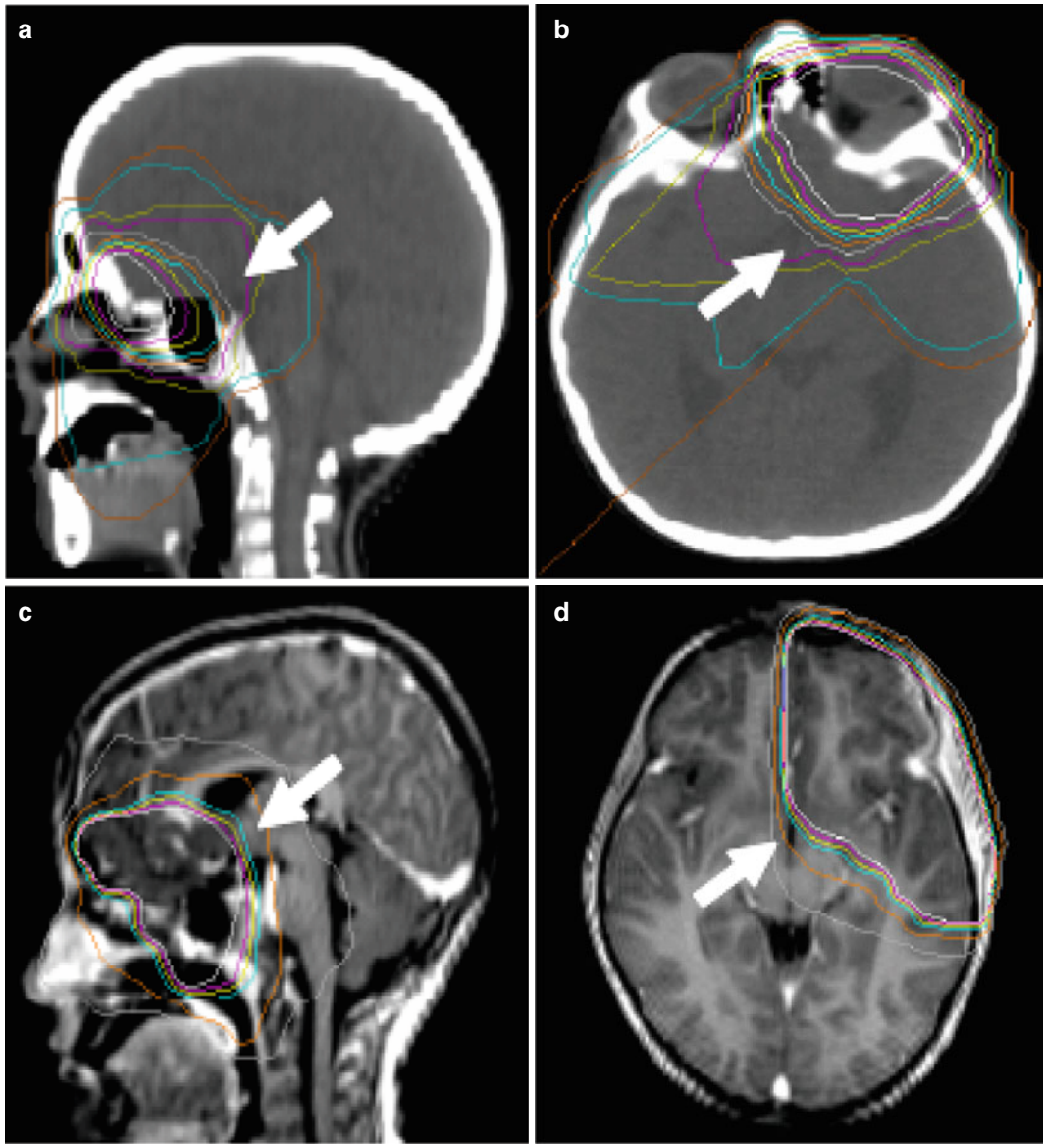

Fig. 5.3 Radiation dosimetry taken from the treatment of children with orbital (**a**, **b**) and infratemporal fossa rhabdomyosarcoma (**c**, **d**). The images illustrate cases in which the HPA is incidentally irradiated and may receive all or a portion of the prescription dose (*arrow* indicates location of the hypothalamus)

flow to sensitive regions of the brain. In one study, 59 children with infratentorial ependymoma underwent provocative testing for GH, thyroid hormone, and ACTH secretion abnormality prior to RT [43]. Abnormal testing was observed in 27 patients (46 %) with 30 % of the 59 having abnormality in GH secretion. Serial measurements of ventricular size from the time of diagnosis to 1 year after RT were recorded and modeled to show that ventricular size at the time of diagnosis could be used to predict pre-irradiation endocrinopathy. Change in ventricular size over time could predict GH deficiency prior to irradiation (Fig. 5.4). This study demonstrated a relatively high rate of pre-irradiation endocrinopathy in a well-defined group, confirming

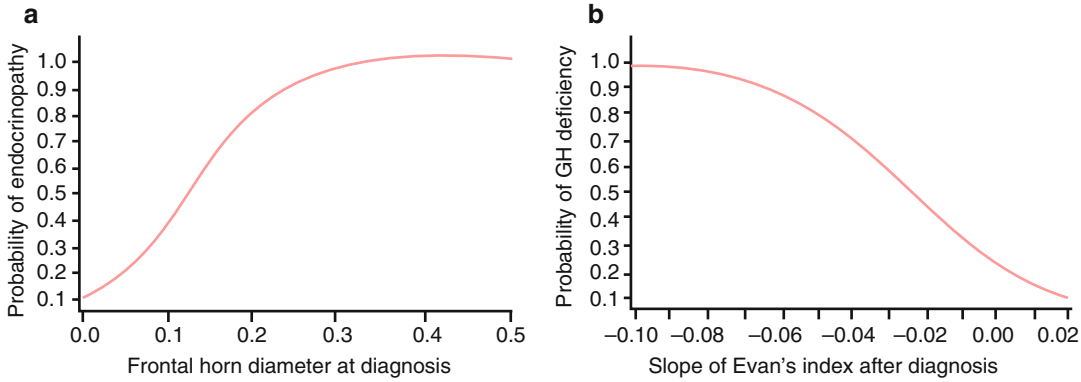

Fig. 5.4 The effect of hydrocephalus on pre-irradiation endocrinopathy in children with infratentorial ependymoma. (**a**) Probability of pre-irradiation endocrine deficiency based on frontal horn diameter measured at diagnosis. (**b**) Probability of pre-irradiation growth hormone (*GH*) deficiency based on change (slope) in the Evan's index after diagnosis. The Evan's index is the ratio of the distance between the most lateral extent of the frontal horns of the lateral ventricles and the width of the parietal brain at the same level

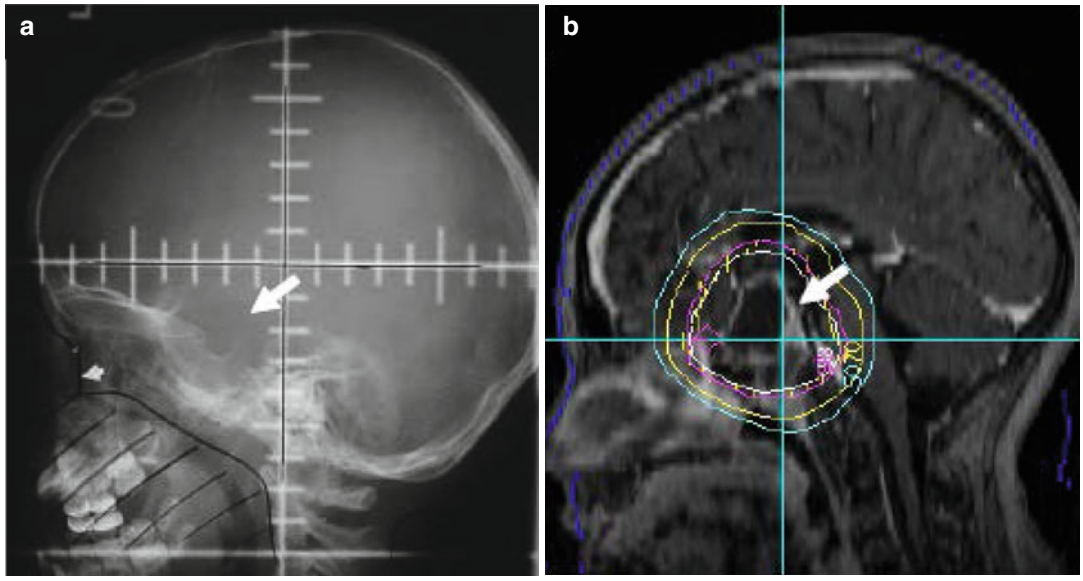

Fig. 5.5 Homogeneous irradiation of the HPA including (**a**) a traditional treatment portal used for cranial irradiation in ALL and (**b**) dosimetry from focal treatment of craniopharyngioma (*arrow* indicates location of the hypothalamus)

another important tumor-related cause of endocrinopathy. Thus, management of hydrocephalus is important, particularly in children with posterior fossa tumors.

Many reports of neuroendocrine effects of RT have used generalized estimates of radiation dose under conditions where the dose to the HPA was relatively homogeneous and discrete [46]. Examples include patients treated with single-dose or fractionated TBI (8–14 Gy), cranial irradiation for leukemia (18 and 24 Gy) and tumors of the sellar or parasellar region in which the HPA was uniformly included in the volume of prescribed dose (>50 Gy) (Fig. 5.5). For other diseases, the HPA may have been located within the irradiated volume for part or all of the treatment or in the gradient of dose (dose fall off) experiencing only a fraction of the daily dose administered (Fig. 5.6).

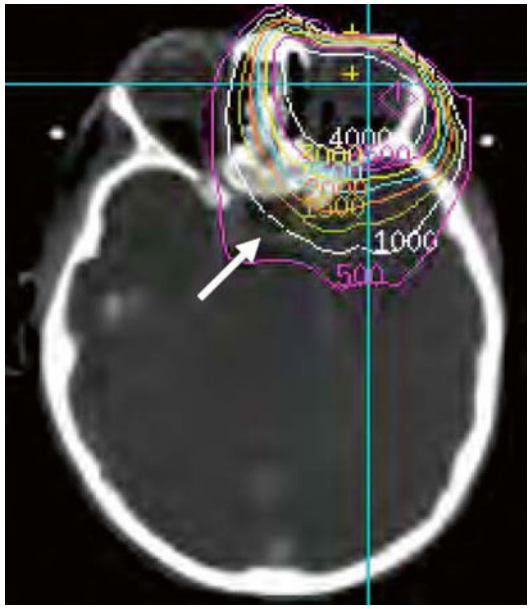

Fig. 5.6 Dosimetry for a typical patient treated with conventional radiation therapy (40 Gy). This example illustrates that the HPA receives only a portion of the total dose given to the primary tumor (*arrow* indicates location of the pituitary)

These circumstances make it difficult to assign a dose to the HPA and to determine the risk for late effects. When the patient is seen by the endocrinologist years after treatment, retrospective dose calculations may be difficult to perform. Newer radiation techniques employ three-dimensional imaging (computed tomography and magnetic resonance, CT and MR) in the planning process. The HPA and other normal tissues can be contoured on CT or MR data and the dose to the HPA calculated and reported more accurately [33]. This information can be correlated with objective measures of endocrine effects and can be used to predict incidence of specific endocrine effects. Already this type of data has been modeled to predict peak GH secretion after radiation therapy [46] and may in the future be used to optimize RT for children (Fig. 5.7, Table 5.3).

In pediatric radiation oncology, reducing side effects of treatment is an important goal. Reducing side effects can be achieved by limiting CNS irradiation to those for whom indications are clear and

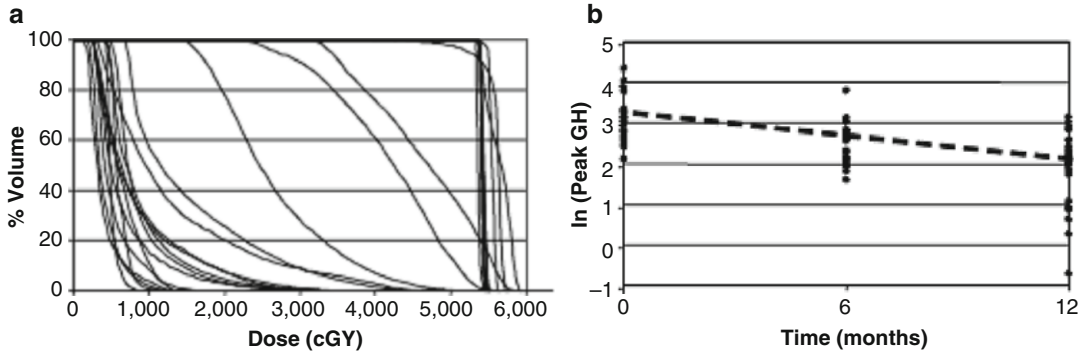

Fig. 5.7 HPA dose-volume data from patients treated with conformal radiation therapy. (**a**) Dose-volume curves represent the percent-volume of the hypothalamus receiving a specific dose. (**b**) Correlation with change in peak GH (ATT/L-dopa) measured before, 6 and 12 months after radiation therapy results in an estimating equation that can be used to predict GH deficiency up to 12 months after irradiation based on the volume (V) received dose over specified intervals. ln [peak GH] = 3.072 − (0.00058 × $V_{0–2,000\ cGy}$ + 0.00106 × $V_{2,000–4,000\ cGy}$ + 0.00156 × $V_{4,000–6,000\ cGy}$) × time

Table 5.3 Probability of growth hormone deficiency according to hypothalamic radiation dose and according to time since irradiation

Hypothalamic radiation dose										
Time (Gy)	15	20	25	30	35	40	45	50	55	60
12 months (%)	17	19	22	25	28	31	34	38	42	45
36 months (%)	26	37	48	59	70	79	86	91	95	97
60 months (%)	39	57	75	87	95	98	99	100	100	100

Adapted from [46]

benefits outweigh the risks. CNS irradiation has been eliminated from treatment of the majority of children with leukemia and a significant proportion of children with low-grade glioma who may be cured with surgery. However, CNS irradiation will remain a mainstay in treatment of most children with brain tumors. Incidental irradiation of the CNS will continue to be observed in children with ocular tumors or tumors of the head and neck. Increased awareness of the importance of the hypothalamus in radiation-related neuroendocrine sequelae, and use of three-dimensional imaging in planning treatment of these tumors, may lead to a reduction in late endocrine effects. Reducing risk for complications can also be achieved by delaying radiation therapy until the child is older or until chemotherapy has had a chance to shrink the tumor and reduce the field of radiation [5, 70], reducing total dose and by reducing volume of irradiation. Dose reductions have been achieved for many tumors including retinoblastoma, pediatric soft tissue sarcomas of the head and neck, and certain CNS tumors including CNS germinoma. Volume reduction has been an important area of research in the treatment of medulloblastoma, ependymoma, low-grade astrocytoma, craniopharyngioma, and CNS germinoma [41, 45]. The risk of treating smaller volumes must be carefully balanced with objective gains documenting reductions in side effects in prospective clinical trials. To this end, the inclusion of endocrinology and its quantitative and relatively objective measures is essential. The risk of endocrine-related complications should be carefully considered in planning radiation therapy, but should not be used as a reason to avoid curative therapy. Careful follow-up and evaluation will lead to early intervention to mitigate consequences of irradiation.

5.3 Clinical Manifestations

5.3.1 GH Deficiency

Altered GH secretion leads to poor growth in childhood cancer survivors, particularly in young children after surgery in the suprasellar region, cranial irradiation [≥18 gray (Gy)], or total body irradiation (≥12 Gy). Hypothalamic function is affected more than is pituitary function. In most patients with GH deficiency, altered hypothalamic GHRH and somatostatin secretion lead to loss of the circadian pulsatile pattern of GH secretion. The radiation effect on GH secretion is dependent on fraction size and total hypothalamic dose-volume [46]. A large fraction size of radiation administered over a short period of time is more likely to cause GH deficiency than is the same total dose administered in smaller fractions over a longer period of time. The peak time for clinical identification of slowed growth consistent with GH deficiency is 3–5 years after such an insult, depending on RT dose. In one prospective study, all of the 21 children treated with a total dose of more than 45 Gy for optic pathway tumor experienced GH deficiency and significant slowing of growth rate within 2 years after irradiation [23]. At doses of cranial irradiation higher than 30 Gy (e.g., for suprasellar or posterior fossa tumor), the risk for GH deficiency may be more than 80 % by 10 years after RT [46]. Cranial irradiation doses greater than 24 Gy result in GH deficiency in as many as two thirds of patients who receive this treatment [13]. In many younger children, GH deficiency results from lower doses (>18 Gy). Doses of only 12–14 Gy of total body irradiation combined with chemotherapy and bone marrow transplantation also pose a significant risk for GH deficiency [13, 36, 37] (Table 5.3).

Growth rate is typically slow in children who are undergoing treatment for cancer and usually improves or shows catch-up after completion of cancer therapy (Fig. 5.8). Children whose growth rate does not improve or whose growth rate is less than the mean for age and gender should be evaluated for growth failure (Fig. 5.9). Causes of slow growth other than GH deficiency include hypothyroidism, radiation damage to growth centers of long bones or spine, chronic unresolved illness, poor nutrition, and depression. In individuals who have attained adult height, GH deficiency may be asymptomatic [24, 78], but alternatively may be associated with easy fatigability, decreased muscle with increased fat mass and truncal adiposity, and increased risk for cardiovascular disease [16, 25].

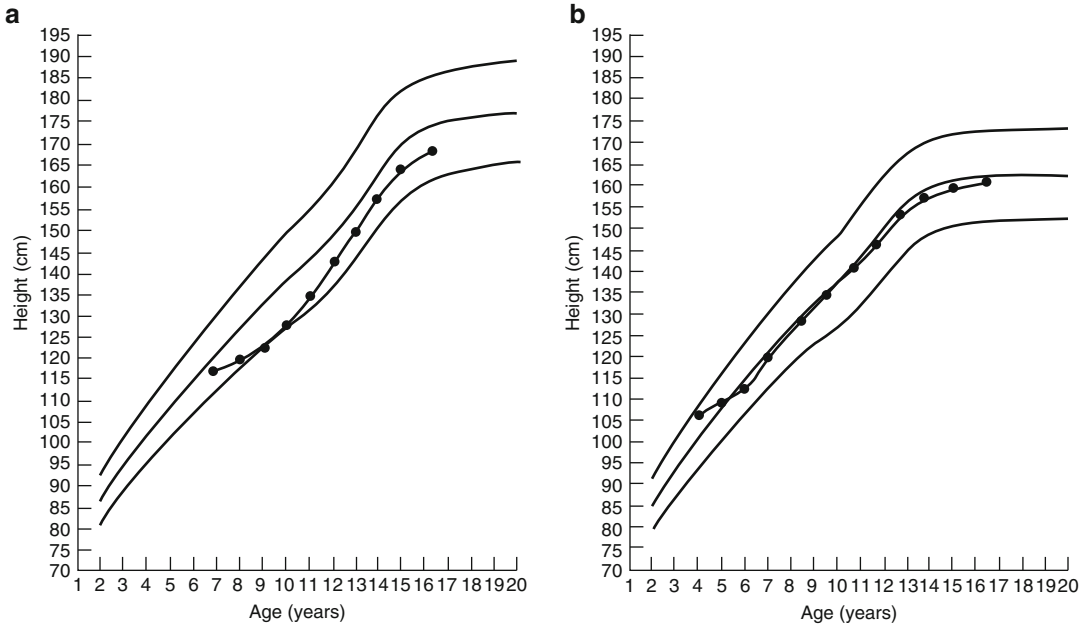

Fig. 5.8 (**a**) Complete catch-up growth in a boy after cancer therapy. (**b**) Growth in a girl after cancer therapy, without catch-up growth. Normal percentiles (5th, 50th, and 95th) as shown are obtained from the National Center for Chronic Disease Prevention and Health Promotion (2000)

5.3.2 LH or FSH Deficiency

High doses of cranial radiation (≥30 Gy) are likely to cause hypothalamic GnRH deficiency and, therefore, gonadotropin deficiency (or in some patients, precocious onset of puberty through loss of inhibition that later progresses to gonadotropin deficiency through loss of GnRH secretory cells). Lower doses of cranial radiation (18–24 Gy) are more likely to cause damage to gamma-aminobutyric-acid-secreting neurons alone (leading to disinhibition and premature activation of GnRH neurons) and, therefore, rapid tempo of puberty or precocious puberty [3, 64]. In girls, the first signs of puberty are growth spurt and breast development (palpable breast buds or thelarche), followed by pubic hair growth and, after about 2 years, by menarche. In boys, the first sign of puberty is testicular enlargement (testes length >2.5 cm), followed by penile and pubic hair growth, followed by a growth spurt. In most studies of normal children, pubertal milestones are attained at ages that are normally distributed, with a standard deviation (SD) of approximately 1 year [76]. Children entering puberty more than 2 SDs earlier or later than average should be considered for endocrine evaluation. The average age that girls experience thelarche is 10 years and that of menarche is about 12 years; the average age when boys experience testicular growth is 11 years.

Patients with gonadotropin deficiency may have delayed, interrupted, or absent puberty. Staging of puberty is usually performed by the criteria of Tanner [76]. In survivors of childhood cancer, we initiate evaluation for delayed puberty in girls with no onset of breast development by 12 years of age or no menarche by 14 years of age and in boys with no sign of testicular growth by 13 years of age. Boys treated with agents that can cause infertility may have normal testosterone and LH concentrations, but reduced testicular volume and elevated FSH because of damage to the seminiferous tubules and reduced sperm production.

5.3.3 Precocious or Rapid Tempo of Puberty

Precocious puberty is defined as the onset of secondary sexual development before age

8 years in girls and before age 9 years in boys [9]. Despite controversy that puberty prior to these ages may occur in normal children [7, 69], younger occurrence of puberty than age 8 or 9 years may be the only clue to the presence of pathology and should not be ignored [48]. Pubic hair, acne, and body odor are not usually part of the presentation of precocious puberty in children younger than 4 years. Precocious puberty occurs in childhood cancer survivors who have lost inhibition of hypothalamic GnRH release as a result of tumor presence, raised intracranial pressure, cranial surgery, or low-dose cranial irradiation (18–24 Gy). Female gender and

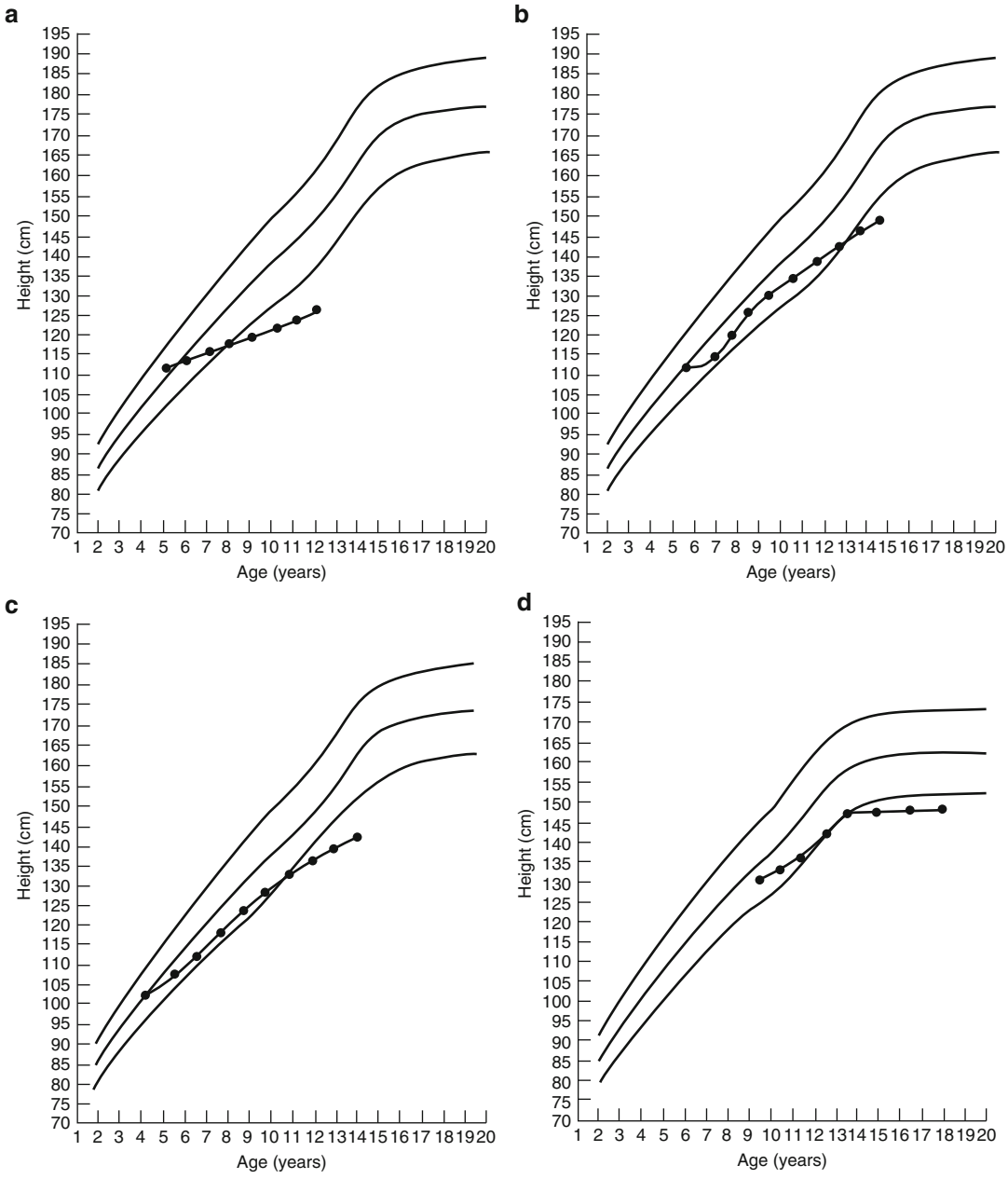

Fig. 5.9 (**a**) Persistent growth failure in a boy after cancer therapy. (**b**) Later growth failure in a girl after recovery of normal growth. (**c**) Subtle persistent growth failure in a boy. (**d**) Growth in a girl with missed GH deficiency. (**e**) Growth in a boy with missed late onset GH deficiency. (**f**) Growth in a girl with central hypothyroidism

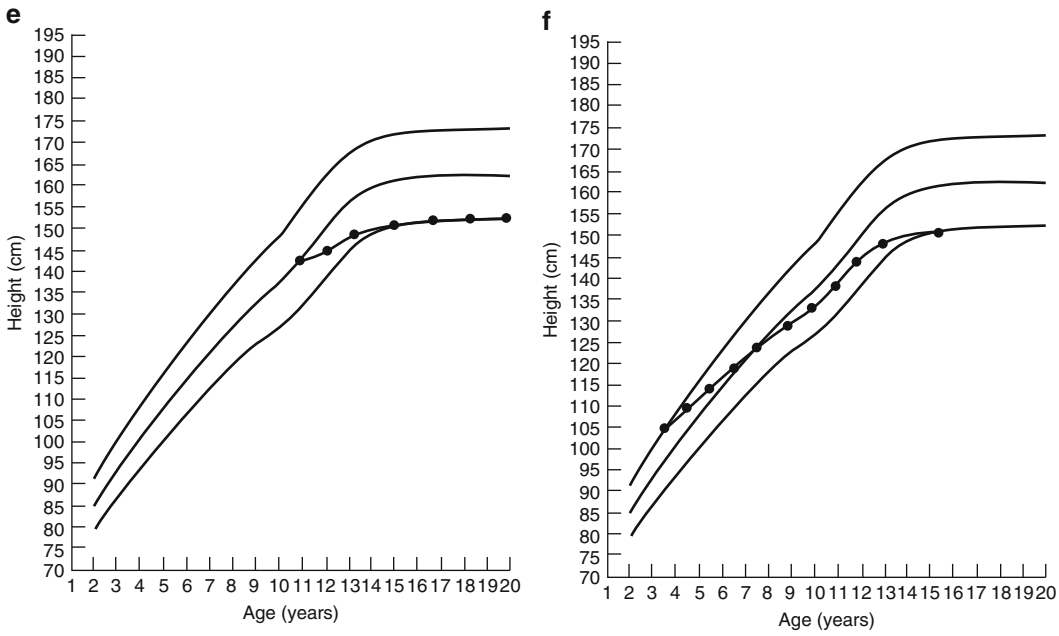

Fig. 5.9 (continued)

younger age at the time of cancer treatment are risk factors for precocious puberty. In some children who have received cranial irradiation, puberty may start at a normal age and advance rapidly. Thus, tempo of progression as well as timing of onset must be monitored. Rapid tempo of puberty is also caused by loss of inhibition of hypothalamic GnRH secretion. The outcome of early onset and/or rapid tempo of puberty can be short adult height and potential emotional lability; early bony maturation causes the child to lose the opportunity for 1–3 years of height growth (Fig. 5.10).

5.3.4 Hypothyroidism

Central hypothyroidism refers to thyroid hormone deficiency caused by a disorder of the pituitary, hypothalamus, or hypothalamic-pituitary portal circulation. In contrast, primary hypothyroidism refers to under-function of the thyroid gland itself.

Primary hypothyroidism is the most common form of hypothyroidism in the general population and may occur in cancer survivors related both to family history and additional contribution from the cancer therapy. In primary hypothyroidism, the thyroid gland may have been injured through irradiation or autoimmune activity, but the central hypothalamic-pituitary-thyroid axis is intact.

In contrast, central hypothyroidism is characterized by blunted or absent nocturnal TSH surge, suggesting the loss of normal circadian variation in TRH release [58]. Central hypothyroidism is difficult to diagnose because of its subtle clinical and laboratory presentation. It is particularly difficult to recognize in patients whose growth is complete, because slowed growth rate can no longer be used as a sign. Symptoms of central hypothyroidism (e.g., asthenia, edema, drowsiness, adynamia, skin dryness) may have a gradual onset and go unrecognized until thyroid replacement therapy is initiated and the patient feels better [22]. In addition to causing delayed puberty and slow growth (Fig. 5.9f), hypothyroidism may cause fatigue, dry skin, constipation, increased sleep requirement, and cold intolerance. Central hypothyroidism was found in as many as 65 % of the survivors of brain or nasopharyngeal tumors, 35 % of bone marrow transplant recipients, and 10–15 % of leukemia survivors [56, 59].

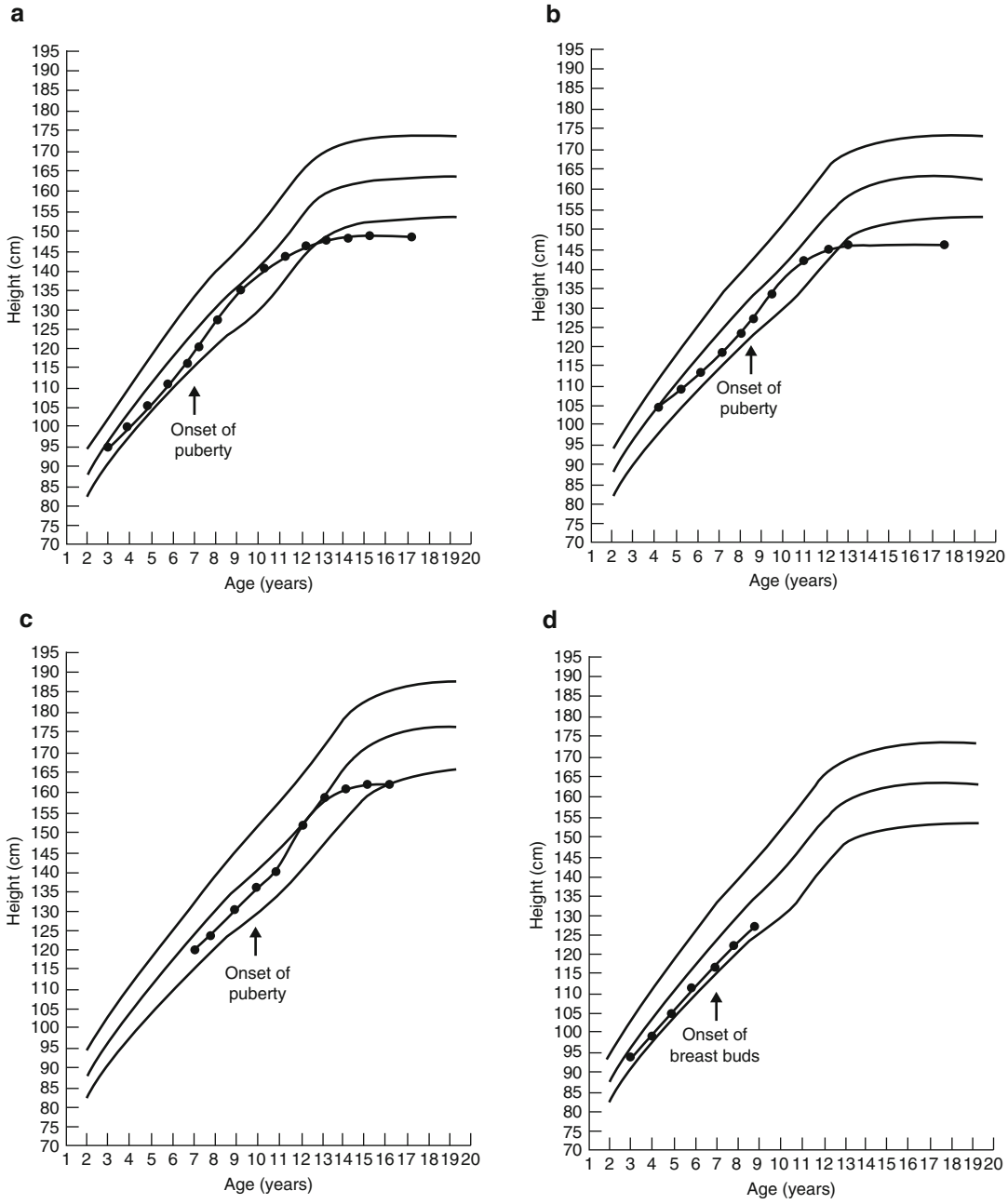

Fig. 5.10 (**a**) Growth in a girl with precocious puberty. (**b**) Growth in a girl with rapid/early puberty. (**c**) Growth in a boy with rapid/early puberty. (**d**) Growth in a girl with GH deficiency hidden by precocious puberty (no growth spurt)

Secretory dysregulation of TSH after irradiation may precede other endocrine disorders. In one cohort of patients with central hypothyroidism, 34 % had dysregulation of TSH secretion before the development of GH deficiency [58, 59].

In cancer survivors, mixed hypothyroidism reflects separate injuries to the thyroid gland and the hypothalamus (e.g., radiation injury to both structures). TSH values are elevated, but in addition, the secretory dynamics of TSH are abnormal with a blunted or absent TSH surge [58, 59].

This is in contrast to primary hypothyroidism in which TSH is elevated and the TSH surge is normal. In a study of 208 childhood cancer survivors referred for evaluation of possible hypothyroidism or hypopituitarism, mixed hypothyroidism was present in 15 (7 %) [59]. All of the patients with mixed hypothyroidism had free T4 concentrations in the low normal range.

5.3.5 ACTH Deficiency

ACTH deficiency is less common than other neuroendocrine deficits but should be suspected in patients who have a history of brain tumor (regardless of therapy modality), cranial irradiation, GH deficiency, or central hypothyroidism [63]. Though uncommon, ACTH deficiency can occur in patients who have received intracranial radiation that did not exceed 24 Gy, but occurs in less than 3 % of patients after chemotherapy alone [62, 63].

Symptoms of central adrenal insufficiency can be subtle and include poor weight gain, anorexia, easy fatigability, and poor stamina. In patients who have ACTH deficiency, as opposed to primary adrenal insufficiency, symptoms of salt craving, electrolyte imbalance, vitiligo, and hyperpigmentation usually are not observed. More overt manifestations of complete ACTH deficiency include weight loss and shakiness that is relieved by eating (hypoglycemia). Signs of adrenal crisis at times of medical stress include weakness, abdominal pain, hypotension, and shock.

Patients with partial ACTH deficiency may have only subtle symptoms unless they become ill. Illness can disrupt these patients' usual homeostasis and cause a more severe, prolonged, or complicated course than expected. As in complete ACTH deficiency, incomplete or unrecognized ACTH deficiency can be life-threatening during concurrent illness. Death during sleep in hypopituitary patients has been proposed to be related to untreated ACTH deficiency [75].

5.3.6 Hyperprolactinemia

Hyperprolactinemia has been described in patients who have received doses of radiation larger than 50 Gy to the hypothalamus or surgery disrupting the integrity of the pituitary stalk. Hyperprolactinemia may result in delayed puberty. In adult women, hyperprolactinemia may cause galactorrhea, menstrual irregularities, loss of libido, hot flashes, infertility, and osteopenia; in adult men, impotence and loss of libido. Primary hypothyroidism may lead to hyperprolactinemia as a result of hyperplasia of thyrotrophs and lactotrophs, presumably due to TRH hypersecretion.

5.3.7 Diabetes Insipidus

Diabetes insipidus may be caused by histiocytosis, germinomas, surgical trauma, or CNS-involved leukemia. Patients with diabetes insipidus usually present with obvious symptoms of excessive thirst and urination with nocturia or enuresis. However, the diabetes insipidus may not be recognized until the patient has dehydration during an intercurrent illness. The urine remains clear in color throughout the day. In patients with CNS-involved leukemia, severe hypernatremic dehydration can occur if the CNS lesion also affects the centers for thirst regulation.

5.3.8 Osteopenia

Osteopenia may result from HPA abnormality (GH deficiency, hypothyroidism, hypogonadism, or hyperprolactinemia) in association with direct effects of glucocorticoid therapy, methotrexate, inactivity, and dietary changes. Osteopenia may present with fractures or may be asymptomatic. Among 141 survivors of childhood leukemia in one study, 30 (21 %) had abnormally low bone mineral density (BMD >1.645 SD below the mean of normal population). Risk factors for bone mineral decrements include male gender, Caucasian race, and cranial irradiation. BMD was inversely correlated with the cumulative dose of cranial irradiation or antimetabolites [31].

5.3.9 Hypothalamic Obesity

Hypothalamic damage from a tumor or cancer treatment can also result in hypothalamic

obesity – unrelenting appetite or weight gain that does not respond to caloric restriction or exercise – attributable to ventromedial hypothalamus damage and abnormality in leptin, ghrelin, and insulin feedback [5, 30]. In rodents, hypothalamic obesity can be suppressed by pancreatic vagotomy to prevent insulin hypersecretion. Insulin hypersecretion is one of the major mechanisms for the development of hypothalamic obesity [5]. In a study of 148 survivors of childhood brain tumors, the risk factors for hypothalamic obesity included age at diagnosis of cancer (<6 years), tumor location (hypothalamic or thalamic), tumor histology (craniopharyngioma, germinoma, optic glioma, prolactinoma, or hypothalamic astrocytoma), hypothalamic irradiation (>51 Gy), and presence of endocrinopathy (deficiency of GH, sex hormones, ACTH, or vasopressin) [5, 38]. No effects were noted on body mass index from ventriculoperitoneal shunting, steroid use (<6 months), or chemotherapy. Thus, hypothalamic damage, due to tumor, surgery, or RT, is the primary risk factor for development of obesity in this patient population (IRHOD.com registry).

5.4 Detection and Screening

5.4.1 Signs and Symptoms Prompting Immediate Evaluation

Survivors of childhood cancer with any of the following ten symptoms should be referred for the evaluation of neuroendocrinopathy: (1) slow growth rate or failure to show catch-up growth, (2) failure to thrive, (3) excessive obesity not thought to be related to steroid therapy, (4) persistent fatigue or anorexia, (5) polydipsia and polyuria, (6) severely dry skin or thin and brittle hair, (7) altered timing of onset of puberty (e.g., signs of puberty before age 9 years or in patients with short height, failure to enter puberty by age 12 years in girls and by 13 years in boys), (8) abnormal tempo of puberty (e.g., rapid or interrupted progression of puberty), (9) galactorrhea, and (10) abnormal menstruation or sexual function.

5.4.2 Surveillance of Asymptomatic Patients

Asymptomatic patients who are at risk for neuroendocrinopathy (Table 5.2) should undergo the following routine yearly surveillance:

- Accurate measurements of height and arm span (an alternative estimate of height, useful if the patient received total body or spinal irradiation or has scoliosis or kyphosis, factors that lead to reduced spinal bone growth or measurement)
- Accurate measurement of weight and assessment of body mass index
- Assessment of nutritional status, adequacy of dietary calcium and vitamin D intake
- Ascertainment of Tanner stage, testicular volume (as measured by Prader orchidometry) or breast development, and interpretation of whether the pubertal status and tempo of progression are appropriate for age and height
- Review of organ systems
- Measurement of serum concentrations of free T4 and TSH
- Low-dose ACTH test if there was tumor in the region of the HPA or cranial irradiation >25 Gy

5.4.3 GH Deficiency

GH deficiency (GHD) should be considered in children who have a slow growth rate and a medical history putting them at risk for GHD [26, 81]. Evaluations should include bone maturation, as determined by radiographic analysis of the left hand and wrist and IGF-I and IGFBP3. The combination of previous cranial or total body irradiation, slow growth rate, normal weight gain, no intercurrent illness, delayed bone maturation, and low plasma levels of IGF-I and IGFBP3 (lower than 1 SD below the mean for the child's age group) are highly suggestive of GHD. The diagnosis should be confirmed by GH stimulation testing [39, 61]. Evaluation of the nocturnal profile of GH secretion is rarely necessary to make the diagnosis, but may be abnormal in symptomatic children after cranial irradiation who have normal stimulated GH results [17].

Recognition of GHD in adults is more difficult, because slow growth rate is not available in them as a marker. Recognition depends on clinical suspicion related to medical history. Diagnosis of GHD in adults requires evidence of other hypothalamic-pituitary hormone deficiencies and a low peak response to GH stimulation tests [24].

5.4.4 LH or FSH Deficiency

During the range of ages when puberty is normally expected to occur, breast development, pubic hair growth and distribution, and vaginal estrogenization should be monitored every 6 months in girls at risk of having LH or FSH deficiencies. Similarly, testes size, pubic hair growth and distribution, and phallus length should be monitored every 6 months in boys. Testicular size in some boys may be small for their genital maturation because of RT- or chemotherapy-induced damage to the seminiferous tubules.

Measurement of bone age, serum LH, FSH, and sex steroid (testosterone or estradiol) should be performed in children with delayed or interrupted progression of puberty. Markers such as inhibin B and anti-Mullerian hormone (AMH) that examine gonadal preservation and fertility are currently under investigation. Data are promising in adults for using inhibin B and AMH in evaluating gonadal health, but their utility in pediatric clinical medicine is still largely unknown.

Evaluation by an endocrinologist should be prompted by the absence of progression of puberty by 1 year after completion of cancer therapy in girls >13 years of age or in boys >14 years of age. Stimulation testing with synthetic GnRH provides more information than does a single, randomly drawn level of LH and FSH. An alternative to a GnRH stimulation test may be a serum sample for LH, FSH, and testosterone or estradiol drawn between 4 and 8 AM, at the time shortly after nighttime pulses of LH have been occurring (Fig. 5.2a).

5.4.5 Precocious Puberty

Precocious puberty is diagnosed if the onset of sexual development is before age 8 years in girls or before age 9 years in boys. A radiograph of the left hand and wrist shows bone age that is advanced compared to chronologic age. However, bone age may be consistent with chronologic age or even delayed in a child who has concurrent GHD or hypothyroidism and who has not undergone a growth spurt (Fig. 5.10d). Since concurrent GHD may not be discovered until after successful treatment of precocious puberty (Fig. 5.10d), we routinely perform provocative GH testing in patients with precocious puberty who have a history of cancer.

5.4.6 Hypothyroidism

Yearly measurements of TSH and free T4 should be done in all patients who have received irradiation (cranial, craniospinal, mantle, or total body irradiation), because the symptoms of central hypothyroidism are often subtle and TSH secretory dysregulation after irradiation may precede other endocrine disorders [59]. The diagnosis of hypothyroidism may be delayed in as many as one third of patients, if TSH secretion is not tested until GHD becomes apparent. Such a delay may be acceptable in a minimally symptomatic adult. In children, however, the potential functional implications of hypothyroidism and lost growth opportunity require early intervention [55]. Early diagnosis of mild hypothyroidism permits early intervention to improve growth velocity and quality of life.

Free T4 and serum TSH are the best screening tests for thyroid status. Sex steroids raise thyroid binding in females and lower thyroid binding in males; however, free T4 tends to remain stable throughout life. In primary hypothyroidism, TSH may rise above 3 mU/L before changes in free T4 are observed. Free T4 below the normal range without TSH elevation is strongly suggestive of central hypothyroidism. However, some patients with central hypothyroidism may have free T4 concentrations in the lowest third of the normal range [55, 59]. The first laboratory evidence of central hypothyroidism may be a small decline in free T4. Central hypothyroidism was often present when the free T4 was in the lowest third of the normal range and TSH was not elevated and could be

confirmed by measurement of the nocturnal TSH surge (hourly TSH at 1500–1800 h and at 2200–0200 h). However, the TSH surge test requires serial sampling and an inpatient hospital admission [58, 59].

Outpatient screening can be accomplished using measurement of TSH at 0800 h (AM) and in the afternoon (PM; between 12 noon and 1800 h) and calculating the ratio. An AM to PM ratio less than 1.3 is consistent with central hypothyroidism [58]. Suppressed TSH on a modest dose of levothyroxine also confirms central hypothyroidism.

If further testing confirms hypothyroidism, treatment should be initiated even though free T4 is still within the normal range because the FT4 is likely to be below the individual's optimal set point.

5.4.7 ACTH Deficiency

For patients at risk for ACTH deficiency (e.g., those who received ≥25 Gy irradiation to HPA), surveillance should include yearly measurement of plasma cortisol concentration at 0800 h and/or a low-dose ACTH test [32]. If cortisol level is below 18 μg/dL (497 nmol/L) at 0800 h, then further evaluation should be directed by an endocrinologist. Measurement of the basal plasma ACTH concentration usually can distinguish primary adrenal disease from central adrenal insufficiency if the ACTH assay is reliable and if there is no urgency in establishing the cause of adrenal insufficiency. Patients with primary adrenal insufficiency have a high concentration of plasma ACTH at 0800 h (as high or higher than 4,000 pg/mL or 880 pmol/L). In contrast, plasma ACTH concentrations are low or low normal in patients with secondary or tertiary adrenal insufficiency. The normal value at 0800 h is usually 20–80 pg/mL (4.5–18 pmol/L).

Patients who present in hypotensive crisis may have adrenal insufficiency or one of several other possible diagnoses. Primary adrenal insufficiency, if present, may have been caused by infection, hemorrhagic diathesis, or metastatic disease to the adrenal gland that requires prompt diagnosis and treatment. In these patients, measurement of basal serum cortisol followed by the low-dose ACTH stimulation test (see below) provides the most rapid and reliable diagnosis. A basal plasma ACTH measurement can be ordered at the same time, but diagnosis and treatment must proceed immediately without waiting for the ACTH and cortisol results.

Patients with partial ACTH deficiency or recent onset of complete ACTH deficiency may have a normal serum cortisol response to high dose of ACTH (250 μg/m^2 by intravenous infusion over 1 min [60] with cortisol measured 1 h later, normally greater than 20 μg/dL (552 nmol/L)). Thus, ACTH deficiency may not be detected by this test.

As a result, the low-dose ACTH test is the most sensitive test for partial ACTH deficiency [32]. In this test, a more physiologic dose of ACTH (1 μg/m^2) is administered by intravenous infusion over 1 min, and blood for a serum cortisol assay is drawn 20 min after the infusion. Peak serum cortisol higher than 20 μg/dL (552 nmol/L) is considered normal, and peak serum cortisol lower than 18 μg/dL (497 nmol/L) is considered low. Patients with cortisol peaks between these values have indeterminate results; these patients should be treated with glucocorticoids when they are ill and will require further evaluation [63]. Further evaluation can include a second low-dose ACTH test or metyrapone administration 2 months to 1 year later.

The low-dose test has supplanted insulin-induced hypoglycemia in many clinical practices. The results are similar to those obtained with insulin-induced hypoglycemia; in addition, ACTH tests can be performed without a physician being present and are less expensive.

5.4.8 Hyperprolactinemia

Hyperprolactinemia is diagnosed when the serum level of PRL is elevated. The PRL level should be periodically measured in patients with symptoms outlined above (Sect. 1.2.6) and in those who received more than 50 Gy of irradiation to the hypothalamus. The definitive PRL level should not be drawn in the hour or two after breast examination or nipple stimulation.

5.4.9 Diabetes Insipidus

Urine specific gravity of patients with diabetes insipidus is usually lower than 1.010 (<300 mOsm/L), unless the patient is severely dehydrated. In most of these patients, serum osmolarity is slightly increased (>300 mOsm/L), the serum sodium may be increased or high normal, and the plasma concentration of antidiuretic hormone is inappropriately low for the osmolarity. However, patients with an intact thirst mechanism may be able to drink sufficiently to avoid laboratory abnormality. Symptoms of polydipsia, polyuria, and nocturia or enuresis may be the only evidence of diabetes insipidus. In partial diabetes insipidus, a water deprivation test may be needed to establish the diagnosis and to rule out other causes of polyuria.

5.4.10 Osteopenia

Osteopenia in cancer survivors may be unrecognized in the absence of fractures unless evaluation is performed. Yearly screening of 25-hydroxyvitamin D may identify dietary vitamin D deficiency, one of the contributors to osteopenia. Identification of low bone mineral requires performance of a dual-energy x-ray absorptiometry (DXA) which offers precise estimates of bone mineral area density (mg/cm^2) at multiple sites for the least amount of radiation exposure. DXA results may require adjustment for height age in a short patient [83]. Quantitative computerized tomography measures true volumetric density (mg/cm^3) of trabecular or cortical bone at any skeletal site of choice. T- and Z-scores may be calculated in reference to normal young adults (age of peak bone mass, 20–35 years) and age-matched normal individuals of the same gender, respectively. T-score should not be used in children or adolescents. Results of DXA must be adjusted for patient height and age.

5.4.11 Hypothalamic Obesity

Clinical symptoms are the basis for diagnosis of hypothalamic obesity. These include rapid weight gain (Fig. 5.11a), voracious appetite, and aggressive food seeking. Patients may have rapid weight gain for other reasons (Fig. 5.11b): exogenous steroid use, inactivity, overfeeding, sympathy of relatives, high thirst, and drinking of sugared drinks. Obesity in adults is defined as having a body mass index (BMI) of ≥30 [BMI = weight (kg)/height (m^2)] (http://www.cdc.gov/obesity/adult/defining.html). Overweight in children is defined as having BMI ≥85th percentile, and obesity defined as BMI ≥95th percentile (http://www.cdc.gov/obesity/childhood/basics.html). Evaluation of overweight patients includes blood pressure measurement, fasting lipid profile, fasting glucose and insulin level, and oral glucose tolerance testing with insulin levels (OGTT). In general, fasting glucose is normal and fasting insulin is elevated in patients with hypothalamic obesity. They have high postprandial insulin level as well as early and rapid and excessive insulin excursions to OGTT. However, these results may be seen in any person who becomes obese.

5.5 Management of Established Problems

5.5.1 GH Deficiency

Growth hormone evaluation usually begins after the first year of treatment completion. Screening labs can help in the diagnosis of growth hormone deficiency, but following a patient's height velocity gives the best insight. There are specific standards for making the diagnosis of growth hormone deficiency. Each varies with age and pubertal status [15, 49].

Standard therapy for GHD is synthetic recombinant human GH (Fig. 5.12a, b). Any patient identified with GHD should be evaluated for possible ACTH deficiency and for central hypothyroidism. If ACTH is deficient, adequate cortisol therapy should be started before GH or thyroid therapy. Patients with GHD who have partial or total ACTH deficiency and are receiving suboptimal hydrocortisone replacement may be at risk of developing symptoms of cortisol deficiency when GH therapy is initiated. This is because of

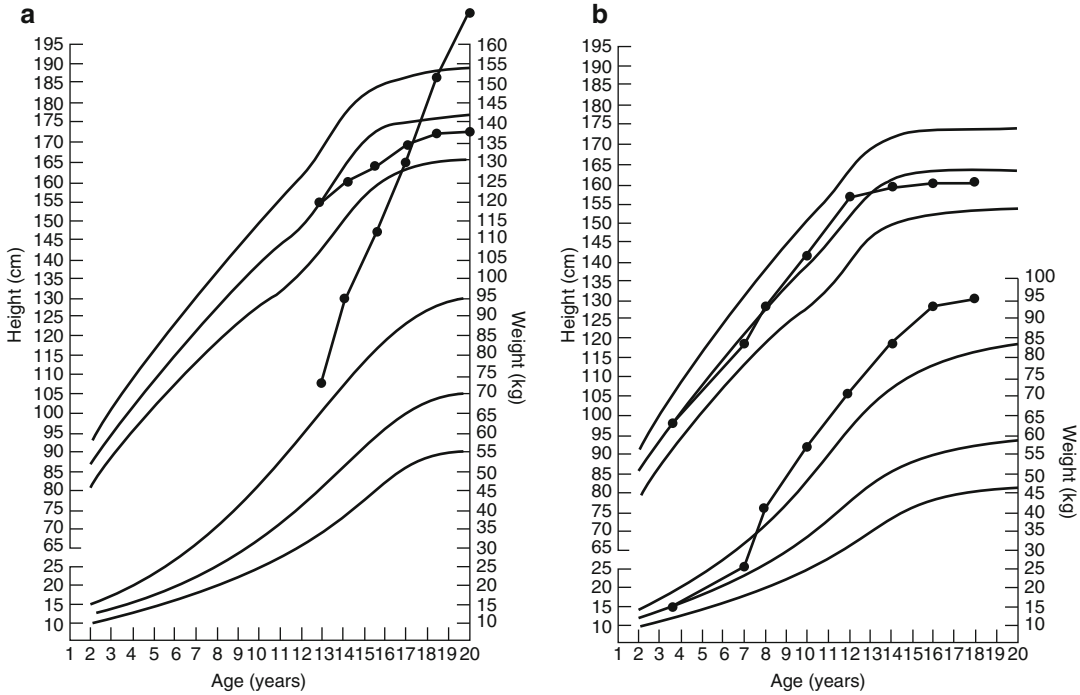

Fig. 5.11 (**a**) Hypothalamic obesity and GH deficiency in a boy. (**b**) Exogenous obesity in a girl

the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1, the enzyme that converts cortisone to cortisol [77].

GH treatment is not recommended during the first year after cancer treatment as this is a time of increased recurrence rates for many tumors. If the history is positive for an aggressive tumor, observation for a longer duration is indicated prior to considering GH therapy, up to 2–3 years after tumor treatment [20, 28, 40].

The endocrinologist and oncologist should discuss and agree upon the decision regarding timing of initiation of GH therapy. The usual dose of GH in children is 0.15–0.3 mg/kg per week divided into daily doses and administered subcutaneously in the evening [15]. IGF-I titration is a method of adjusting GH dosing that allows for strict control of statural growth while reducing the risk for possible side effects associated with overtreatment. In patients with a tumor history, maintaining an IGF-I level between the 20th and 80th percentile for age is recommended. This range of GH dosing should support normal growth velocity (not catch-up growth) in patients who could potentially have adverse effects from even mild overtreatment. Lower doses are used in adults [78].

Each injection of GH produces a pharmacologic level of GH for approximately 12 h. The growth rate in children receiving ongoing GH therapy typically increases to above normal for 1–3 years and then slows to normal velocity. After 4–5 years of GH therapy, the adult height SD scores of leukemia survivors with GHD usually approached the height SD scores at the time of tumor diagnosis [37]. The growth response may be poorer in patients who have received total body or spinal irradiation or in patients with particular diseases such as neuroblastoma [29, 53].

During GH therapy, evaluation of the growth response and adjustment of GH dose should occur every 4–6 months and include measurement of height, weight, and arm span. Arm span is a surrogate measure of height, particularly in patients in whom height measurement may not fully reflect body growth (e.g., those with scoliosis or a history of spinal irradiation). GH dose can be increased as weight gain occurs to maintain a stable dose per kilogram of body weight. Serum IGF-I measurements are recommended every

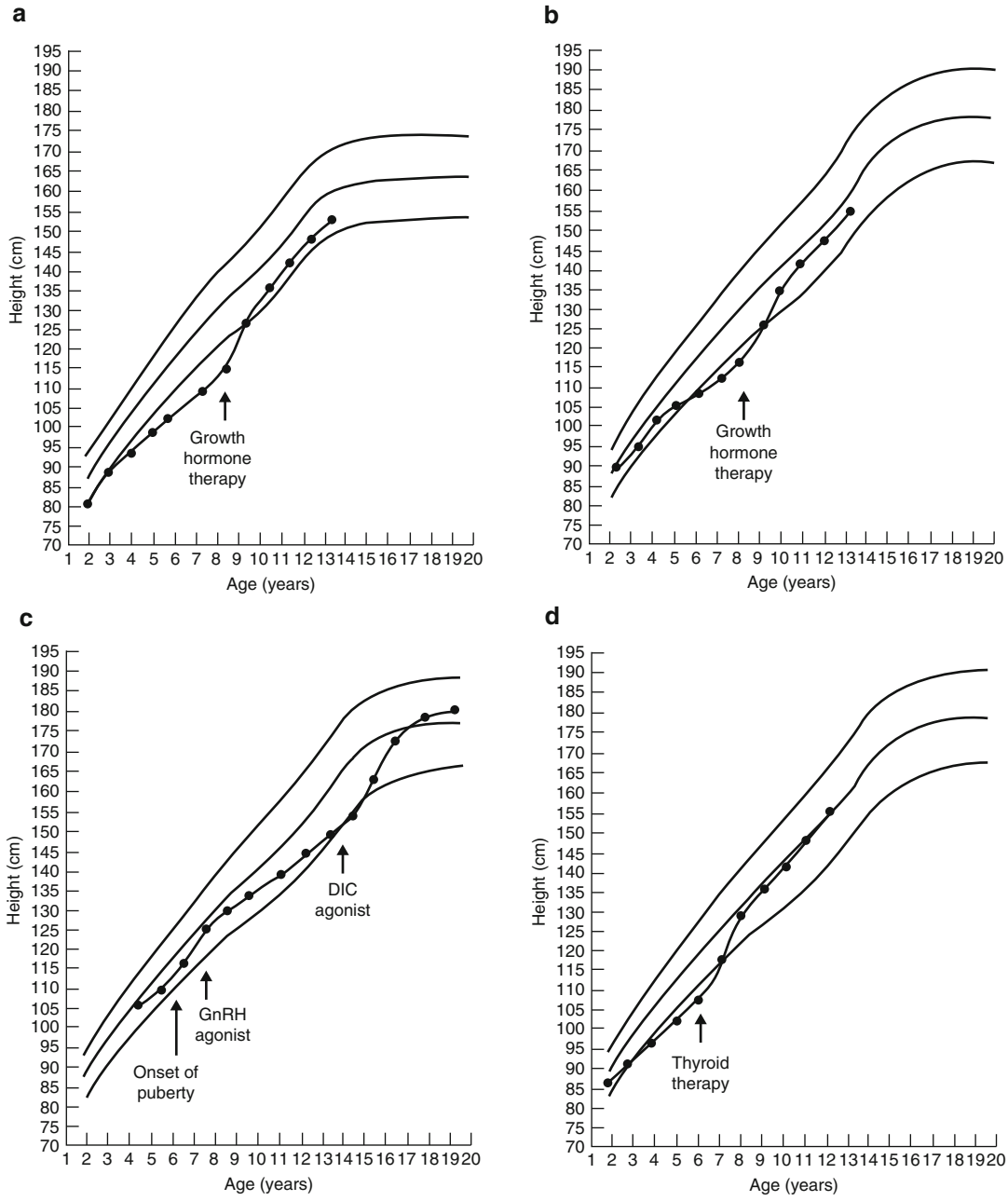

Fig. 5.12 (**a**) Response to GH therapy in a girl with GH deficiency. (**b**) Response to GH therapy in a boy with GH deficiency. (**c**) Response to GnRH agonist in a boy with precocious puberty. (**d**) Response to thyroid hormone in a boy with central hypothyroidism

4–6 months in the growing years and a minimum of yearly once an adult height has been reached [26]. After the first 1–2 years of GH therapy, if the level of IGF-I surpasses the upper limits of normal for the patient's age and gender, the GH dose should be decreased to achieve an IGF-I near the mean for age and gender. Evaluation of pubertal stage and screening for development of additional

endocrinopathies (thyroid, gonadotropins, ACTH) should continue to be performed at least annually. Even with GH therapy, some childhood cancer survivors do not grow as well as expected, a finding that suggests that other factors, such as thyroid hormone deficiency, are present.

GH treatment in children is usually safe [11, 15, 66, 81]. Adverse effects are rare, occur soon after therapy is initiated, and include pancreatitis, benign intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis [50], and carpal tunnel syndrome [8]. Pseudotumor cerebri and carpal tunnel syndrome are probably caused by sodium and water retention. An increase in the growth and pigmentation of nevi also has been described [10]. GH therapy does not increase the risk of brain tumor or leukemia recurrence [4, 20, 37, 74]. GH therapy also did not appear to increase the risk of secondary leukemia or solid malignancy in patients who did not received RT in the Childhood Cancer Survivor Study [20]. Because all of the evaluable patients who developed a second neoplasm in this study had received RT, synergistic effects of GH and irradiation on the development of second malignancy could not be discerned [20]. The absolute number of excess solid tumors attributable to GH (including benign meningiomas), if any, will probably be very small (<4/1,000 person years at 15 years after diagnosis).

5.5.2 LH or FSH Deficiency

The use of estrogen or testosterone therapy should not be initiated without careful attention to the pediatric survivor's growth pattern. Replacement of pubertal hormones in a short or slowly growing adolescent can cause fusion of bony growth centers and shorter-than-expected adult height. Such therapy should be provided only in coordination with the pediatric endocrinologist after assessment of growth potential and treatment of GH or thyroid deficiencies. Initiation of sex steroid therapy in a short adolescent may be delayed until age 15 years to permit response to GH or thyroid hormone therapy and taller adult height. In short adolescents with delayed puberty, a few years of therapy with low-dose sex steroid therapy is preferable to full replacement. Such doses simulate the sex steroid levels observed in the first year or so of puberty and are less likely than full sex steroid replacement to cause inappropriate maturation of bone age. Girls can be treated with the conjugated estrogen tablets Premarin® (0.3 mg every other day), ethinyl estradiol (5 mcg daily, one quarter of a 20-mcg tablet daily), or half of a low-dose estrogen patch changed half as often as in adults [79]. Menstrual spotting can be treated monthly or 3-monthly with medroxyprogesterone 10 mg per day for 10 days without a break in estrogen therapy. Boys can be treated with 45- or 50-mg/m^2 testosterone cypionate injected intramuscularly once each month or with topical testosterone gel 0.5–1.25 g daily. After achievement of height acceptable to the patient, both boys and girls may benefit from a gradual increase in hormone replacement therapy to the full replacement dose, if there has been no sex steroid production in recent months. The increase to full replacement should take place in 1- to 3-month steps to permit gradual adjustment to the hormonal effects.

Full hormone replacement in adolescent girls who have reached their adult height is easily achieved with regular use of a standard oral contraceptive (28-day or 3-month pill packet) or estrogen patch (used especially if the girl is on GH therapy). Boys who have attained their adult height can be treated with testosterone (200 mg injected intramuscularly every 2 weeks) or with androgen by patch or by topical gel (about 5 g daily).

One medical risk of delayed puberty is delayed bone mineralization. Adolescents with delayed or interrupted puberty should receive 1,500 mg of elemental calcium and 1,000 IU of vitamin D per day to improve bone mineralization.

5.5.3 Precocious Puberty

GnRH analogues are the most effective treatments for precocious puberty, rapid tempo puberty, or normally timed puberty that is inappropriate for height. GnRH analogues suppress

LH and FSH release from the pituitary gland through the provision of a steady rather than a pulsatile level of GnRH; the pituitary gland stops responding to GnRH when GnRH concentrations are steady or unchanging. The use of GnRH analogues to delay pubertal progression optimizes adult height potential by permitting the child to grow taller without experiencing a rapid change in bone maturation [47] (Fig. 5.12c).

Treatment with GnRH analogues should be prescribed and monitored by a pediatric endocrinologist [82]. GnRH analogues can be administered as a daily subcutaneous injection. More commonly, a sustained or depot preparation is used – monthly, every 3 months, every 6 months, or as a yearly subcutaneous implant [35, 52, 54]. GnRH analogue therapy is usually continued at least until patients attain the third percentile for adult height: 152 cm (60 in.) in girls and 162 cm (64 in.) in boys.

5.5.4 Hypothyroidism

Standard treatment for central hypothyroidism or for primary hypothyroidism is levothyroxine replacement therapy (Fig. 5.12d). Thyroid hormone replacement can precipitate clinical decompensation in patients with unrecognized adrenal insufficiency, because levothyroxine treatment increases metabolic clearance of cortisol. Thus, it is necessary to evaluate patients for adrenal insufficiency and, if present, treat with hydrocortisone before initiating thyroid hormone therapy. In patients who also have ACTH deficiency, we usually initiate cortisol replacement 3 days before beginning thyroid hormone therapy.

The typical thyroid hormone replacement dose for infants under 3 years of age is levothyroxine 5–10 mcg/kg/day, and for healthy children and adolescents with TSH less than 30 mU/L is 3 mcg/kg by mouth every morning. Children over 3 years of age who have TSH greater than 30 mU/L, or about whom there are concerns about medical stability, can begin levothyroxine at a low dose (0.75 mcg/kg by mouth every morning for a month) and have it further increased by 0.75 mcg/kg per day each month to permit more gradual physiologic and psychologic adjustment to the new metabolic state. Thyroid hormone concentrations should be measured after 4 weeks of therapy or 4 weeks after any dose change, because levothyroxine has a long half-life (5–6 days).

Unlike primary hypothyroidism, it is not useful to monitor TSH in patients with central hypothyroidism. In one prospective study of 37 patients with central hypothyroidism, free T4 and free T3 were monitored during therapy, and dose was adjusted to achieve free T4 in the midnormal range without free T3 elevation and without symptoms of hypothyroidism or hyperthyroidism [22]. We usually adjust thyroid hormone replacement therapy in patients with central hypothyroidism to maintain the level of free T4 just above the middle of the normal range (e.g., free T4 of 1.4–1.6 ng/dL if the normal range is 0.78–1.85 ng/dL or free T4 of 2.2–2.4 if the normal range is 1.0–2.8 ng/dL).

5.5.5 ACTH Deficiency

Patients with ACTH insufficiency require daily hydrocortisone replacement. Hydrocortisone is the preferred glucocorticoid for replacement in children, because it is least likely to impair growth. Patients with ACTH deficiency do not need mineralocorticoid replacement, because these hormones are produced by the adrenal gland under the influence of the renin-aldosterone system rather than under the influence of ACTH. Dexamethasone is not standard for glucocorticoid replacement therapy in children and adolescents because it has greater potential to suppress growth than does hydrocortisone.

The dose of hydrocortisone for replacement therapy is 7–10 mg/m^2 per day, divided into two or three doses administered by mouth. For example, a child whose body surface is 0.9 m^2 could receive 2.5 mg three times per day, or an adult whose body surface is 1.5 m^2 could receive 5 mg at breakfast and at 1500 h plus 2.5 mg at bedtime. The glucocorticoid dose may need to be increased in patients taking drugs that accelerate hepatic steroid metabolism such as phenytoin, barbitu-

rates, newer anticonvulsants, rifampin, mitotane, and aminoglutethimide [19]. Patients with GHD who have partial or total ACTH deficiency and are receiving suboptimal cortisol or cortisone replacement may be at risk of developing symptoms of cortisol deficiency when GH therapy is initiated. This is because of the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1. Similarly, the initiation of thyroid hormone therapy in a child with unrecognized or undertreated ACTH deficiency also can precipitate adrenal crisis.

Patients with ACTH deficiency must receive "stress dosing": additional glucocorticoid during times of illness or stress (e.g., fever, gastrointestinal illness, injury). The dose of additional hydrocortisone necessary during times of illness is 30 mg/m^2 per day divided into doses every 8 h administered by mouth. Patients whose illness or injury is severe enough to require emergency care or hospitalization, who are unable to retain oral medication, or who require anesthesia or surgery should urgently receive hydrocortisone (50–100 mg/m^2 intramuscularly or intravenously), followed by hydrocortisone (10–25 mg/m^2 intravenously every 6 h) during management of the critical illness [63]. At stress doses, hydrocortisone provides some mineralocorticoid effect. The hydrocortisone dose should be reduced to the usual replacement therapy dose as soon as the event is over or the patient's medical status improves. Tapering of the dose is not necessary if the pharmacologic stress doses are used for less than 10 days.

Patient and family education is an important component of treating patients with ACTH deficiency. The patient and responsible family members should be instructed about the following issues:

- The nature of the hormonal deficit and the rationale for replacement therapy
- Maintenance medications and the need for changes in medications during minor illnesses
- When to consult a physician
- The need to keep an emergency supply of glucocorticoids
- The proper *stress* dose for the patient's body weight
- When and how to inject glucocorticoids for emergencies

Every patient should have at least two preprepared syringes of hydrocortisone (Solu-Cortef®): one at home and one at work or school. In addition, it is wise for the patient to carry such a syringe at all times. The syringes can be obtained as 100-mg/2-mL vials ("Activial") or can be prepared by a pharmacist in regular 1-mL syringes from a multidose vial. The patient and parents must be instructed regarding the correct dose. The injectable stress dose is five to ten times the daily hydrocortisone dose. Thus, typical doses for children would be 50 mg (0.5 mL of a 100-mg/2-mL solution). Unused syringes should be replaced each year or if the solution inside becomes cloudy or colored.

The patient and one or more responsible family or household members should be instructed to inject the contents of a syringe subcutaneously or intramuscularly anywhere on the patient's body during any one of the following circumstances:

- The patient has a major injury with substantial blood loss (more than one cup), fracture, or neurogenic shock.
- The patient has nausea and vomiting and cannot retain oral medications.
- The patient has symptoms of acute adrenal insufficiency, such as hypotension or hypoglycemia.
- The patient is found unresponsive.

Instructions should include the need to obtain medical help immediately after the injection of the stress dose. The patient should be instructed to have a low threshold for injecting the hydrocortisone: if the patient feels the injection *might* be necessary, then it *should* be injected, and medical attention should be sought. It is unlikely, however, that a patient will need the stress dose of hydrocortisone more than two or three times per year, and most patients go for

years without needing it. Used hydrocortisone syringes should be replaced immediately.

Every patient should wear a medical alert (MedicAlert®) bracelet or necklace and carry the emergency medical information card that is supplied with it. Both should indicate the diagnosis, the daily medications and doses, and the physician to call in the event of an emergency. Patients can enroll in MedicAlert by calling 800-432-5372 or through the internet at www.medicalert.org (USA) or www.medicalert.ca (Canada).

5.5.6 Hyperprolactinemia

Prolactin elevation in excess of 100 ng/mL may lead to symptoms. Dopamine agonists such as bromocriptine and cabergoline are the treatment of choice to suppress PRL secretion and to restore normal gonadal function. Cabergoline is, in general, more potent, much longer acting, and better tolerated than bromocriptine. The usual starting dose is 0.25 mg twice a week. High doses such as those used in Parkinson disease have been associated with cardiac valvular problems [2]. However, typical doses used for hyperprolactinemia have not demonstrated such risks [73].

5.5.7 Diabetes Insipidus

Hormone replacement in diabetes insipidus is desmopressin acetate or DDAVP®, which can be given by subcutaneous injection, by nasal insufflation, or orally in one or two daily doses. Oral desmopressin is available in tablets containing 0.1 or 0.2 mg. To avoid water intoxication, successive doses should not be given until a brief diuresis has occurred at least once daily. By giving a dose at bedtime, sleep disturbance by nocturia can be avoided. The usual dose of 1.0–5.0 μg intranasally, or 0.1–0.8 mg orally, will usually achieve rapid urinary concentration that lasts approximately 8–24 h (Fig. 5.13). The process of starting desmopressin therapy may require close monitoring of volume of fluid taken in and urine output. Several weeks of dose adjustment may be required before achieving a stable dose (Fig. 5.13). In patients with partial diabetes insipidus, chlorpropamide may be used to enhance the effect of the limited antidiuretic hormone that remains.

5.5.8 Osteopenia

Osteopenia after cancer therapy may be prevented by maintaining optimal calcium (1,500 mg daily) and vitamin D (1,000 units daily) in the diet. Nutritional supplements may be needed in cases of osteopenia unresponsive to behavioral and dietary management. In addition, early diagnosis and replacement of hormone deficiencies will benefit bone mineralization. In the event of fractures, bisphosphonate therapy (oral or intravenous) may be beneficial.

5.5.9 Hypothalamic Obesity

Part of the therapy for hypothalamic obesity involves early identification and initiation of preventive measures including caloric and dietary control and maintenance of regular exercise. In addition to maintaining these lifestyle choices, several therapies have been used pragmatically or in research efforts. These include dexedrine, ritalin, metformin, and octreotide [6, 21]. Dexedrine and ritalin are taken orally and act as stimulants with the side effect of appetite suppression (in this situation, beneficial). Metformin is taken orally once or twice daily, acts as a sensitizer to insulin effects, and may serve to probe the etiology of obesity in individual patient. If the obesity is exogenous and hyperinsulinemia is a consequence of the obesity and insulin resistance, lifestyle changes with or without metformin may resolve obesity. If the obesity is hypothalamic and the hyperinsulinism is the cause of the increased appetite, metformin use may lead to hypoglycemia and no reduction of striving for food. Octreotide is a somatostatin analogue that binds to the somatostatin receptor. It serves to decrease not only insulin secretion from pancreatic β-cells, but also growth hormone and TSH secretion from the pituitary gland. If the obesity is exogenous and high insulin levels reflect insulin resistance,

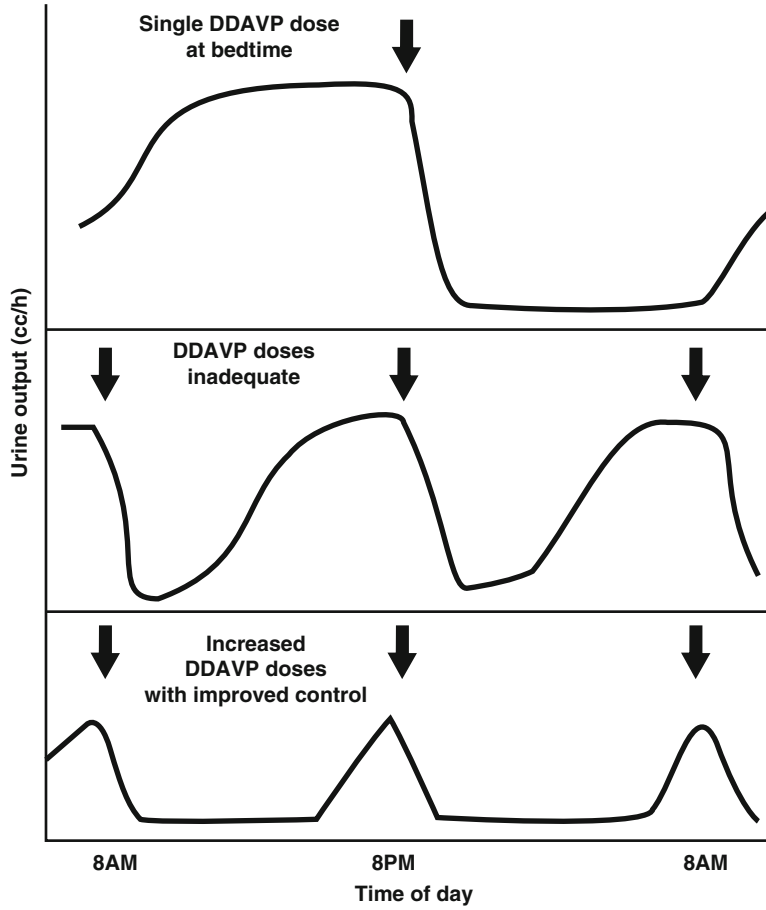

Fig. 5.13 Urine output with inadequate DDAVP treatment (*top* and *middle panels*) and improved control of urine output with adjusted DDAVP dosing (*bottom panel*)

the patient may become diabetic with octreotide therapy. If the obesity is hypothalamic, octreotide will decrease insulin secretion leading to reduced appetite, weight control, and improved sense of well-being [5, 38]. Octreotide is taken as two or three injections daily. Side effects of octreotide may include gallstones. Patients treated with octreotide may also require therapy with growth hormone and thyroid hormone.

Bariatric surgery has been reported to be beneficial in selected patients [30, 65, 80]. Additional research is needed in order to identify optimal treatment modalities in order to control weight in hypothalamic obesity. An international internet registry (IRHOD.com) has been developed for patients to self-register, in order to be considered for participation in research projects. Investigators can also register on this site to apply for research access to the database.

References

1. Agha A, Sherlock M, Brennan S et al (2005) Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab 90:6355–6360
2. Antonini A, Poewe W (2007) Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol 6:826–829
3. Armstrong GT, Chow EJ, Sklar CA (2009) Alterations in pubertal timing following therapy for childhood malignancies. Endocr Dev 15:25–39
4. Bell J, Parker KL, Swinford RD et al (2010) Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 95:167–177
5. Bereket A, Kiess W, Lustig RH et al (2012) Hypothalamic obesity in children. Obes Rev. doi:10.1111/j.1467-789X.2012.01004.x
6. Bingham NC, Rose SR, Inge TH (2012) Bariatric surgery in hypothalamic obesity. Front Endocrinol (Lausanne) 3:23
7. Biro FM, Galvez MP, Greenspan LC et al (2010) Pubertal assessment method and baseline characteristics

in a mixed longitudinal study of girls. Pediatrics 126:e583–e950
8. Blethen SL, Allen DB, Graves D et al (1996) Safety of recombinant deoxyribonucleic acid-derived growth hormone: the National Cooperative Growth Study experience. J Clin Endocrinol Metab 81:1704–1710
9. Boepple PA, Crowley WF Jr (1996) Precocious puberty. In: Adashi EY, Rock JA, Rosenwaks Z (eds) Reproductive endocrinology, surgery, and technology, vol 1. Lippincott-Raven, Philadelphia, p 989
10. Bourguignon JP, Pierard GE, Ernould C et al (1993) Effects of human growth hormone therapy on melanocytic naevi. Lancet 341:1505–1506
11. Carel JC, Ecosse E, Landier F et al (2012) Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 97:416–425
12. Castaño JP, Delgado-Niebla E, Durán-Prado M et al (2005) New insights in the mechanism by which SRIF influences GH secretion. J Endocrinol Invest 28(5 Suppl):10–13
13. Chemaitilly W, Sklar CA (2010) Endocrine complications in long-term survivors of childhood cancers. Endocrinol Relat Cancer 17(3):R141–R159
14. Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332:1351–1362
15. Cook DM, Rose SR (2012) A review of guidelines for use of growth hormone in pediatric and transition patients. Pituitary 15(3):301–310
16. Cummings DE, Merriam GR (2003) Growth hormone therapy in adults. Annu Rev Med 54:513–533
17. Darzy KH, Pezzoli SS, Thorner MO, Shalet SM (2005) The dynamics of growth hormone (GH) secretion in adult cancer survivors with severe GH deficiency acquired after brain irradiation in childhood for nonpituitary brain tumors: evidence for preserved pulsatility and diurnal variation with increased secretory disorderliness. J Clin Endocrinol Metab 90:2794–2803
18. Darzy KH, Shalet SM (2009) Hypopituitarism following radiotherapy. Pituitary 12:40–50
19. Elias AN, Gwinup G (1980) Effects of some clinically encountered drugs on steroid synthesis and degradation. Metabolism 29:582–592
20. Ergun-Longmire B, Mertens AC, Mitby P et al (2006) Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab 91:3494–3498
21. Eyal O, Sundararajan S, Inge TH, Rose SR (2006) Obesity in patients with craniopharyngioma. Endocrinologist 16:286–293
22. Ferretti E, Persani L, Jaffrain-Rea ML et al (1999) Evaluation of the adequacy of levothyroxine replacement in patients with central hypothyroidism. J Clin Endocrinol Metab 84:924–929
23. Fouladi M, Wallace D, Langston JW et al (2003) Survival and functional outcome of children with hypothalamic/chiasmatic tumors. Cancer 97:1084–1092
24. Ghigo E, Aimaretti G, Corneli G (2008) Diagnosis of adult GH deficiency. Growth Horm IGF Res 18:1–16
25. Gilchrist FJ, Murray RD, Shalet SM (2002) The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. Clin Endocrinol (Oxf) 57:363–370
26. Growth Hormone Research Society (2000) Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 85:3990–3993
27. Gurney JG, Ness KK, Sibley SD et al (2006) Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer 107:1303–1312
28. Hartman ML, Xu R, Crowe BJ et al (2013) Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. J Clin Endocrinol Metab 98:980–988
29. Hovi L, Saarinen-Pihkala UM, Vettenranta K et al (1999) Growth in children with poor-risk neuroblastoma after regimens with or without total body irradiation in preparation for autologous bone marrow transplantation. Bone Marrow Transplant 24:1131–1136
30. Inge TH, Pfluger P, Zeller M et al (2007) Gastric bypass for treatment of hypothalamic obesity after craniopharyngioma therapy. Nat Clin Pract Endocrinol Metab 3:606–609
31. Kaste SC, Rai SN, Fleming K et al (2006) Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 46:77–87
32. Kazlauskaite R, Evans AT, Villabona CV et al (2008) Corticotropin tests for hypothalamic-pituitary adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab 93:4245–4253
33. Laughton SJ, Merchant TE, Sklar CA et al (2008) Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol 26:1112–1118
34. Lee KO, Persani L, Tan M et al (1995) Thyrotropin with decreased biological activity, a delayed consequence of cranial irradiation for nasopharyngeal carcinoma. J Endocrinol Invest 18:800–805
35. Lee PA, Klein K, Mauras N et al (2012) Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty. J Clin Endocrinol Metab 97:1572–1580
36. Leung W, Hudson MM, Strickland DK et al (2000) Late effects of treatment in survivors of childhood acute myeloid leukemia. J Clin Oncol 18:3273–3279
37. Leung W, Rose SR, Zhou Y et al (2002) Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 20:2959–2964

38. Lustig RH, Post SR, Srivannaboon K et al (2003) Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 88:611–616
39. May M, Rose SR (2007) Oral hydration during growth hormone stimulation with clonidine. J Pediatr Nurs 22:383–387
40. Mackenzie S, Craven T, Gattamaneni HR et al (2011) Long-term safety of growth hormone replacement after CNS irradiation. J Clin Endocrinol Metab 96:2756–2761
41. Merchant TE, Pritchard DL, Vargo JA, Sontag MR (2001) Radiation therapy for the treatment of childhood medulloblastoma: the rationale for current techniques, strategies, and dose-volume considerations. Electro Medica 69:69–71
42. Merchant TE, Kiehna EN, Sanford RA et al (2002) Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. Int J Radiat Oncol Biol Phys 53:533–542
43. Merchant TE, Zhu Y, Thompson SJ et al (2002) Preliminary results from a phase II trial of conformal radiation therapy for pediatric patients with localized low-grade astrocytoma and ependymoma. Int J Radiat Oncol Biol Phys 52:325–332
44. Merchant TE, Williams T, Smith JM et al (2002) Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. Int J Radiat Oncol Biol Phys 54:45–50
45. Merchant TE, Kun LE, Krasin MJ et al (2008) Multiinstitution prospective trial of reduced-dose craniospinal irradiation (23.4 Gy) followed by conformal posterior fossa (36 Gy) and primary site irradiation (55.8 Gy) and dose-intensive chemotherapy for average-risk medulloblastoma. Int J Radiat Oncol Biol Phys 70(3):782–787
46. Merchant TE, Rose SR, Bosley C et al (2011) Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. J Clin Oncol 29:4776–4780
47. Mericq MV, Eggers M, Avila A et al (2000) Near final height in pubertal growth hormone (GH)-deficient patients treated with GH alone or in combination with luteinizing hormone-releasing hormone analog: results of a prospective, randomized trial. J Clin Endocrinol Metab 85:569–573
48. Midyett LK, Moore WV, Jacobson JD (2003) Are pubertal changes in girls before age 8 benign? Pediatrics 111:47–51
49. Molitch ME, Clemmons DR, Malozowski S et al (2011) Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1587–1609
50. Mostoufi-Moab S, Isaacoff EJ, Spiegel D et al (2013) Childhood cancer survivors exposed to total body irradiation are at significant risk for slipped capital femoral epiphysis during recombinant growth hormone therapy. Pediatr Blood Cancer 60:1766–1771
51. Nass R, Gaylinn BD, Thorner MO (2011) The role of ghrelin in GH secretion and GH disorders. Mol Cell Endocrinol 340:10–14
52. Neely EK, Lee PA, Bloch CA et al (2010) Leuprolide acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. Int J Pediatr Endocrinol 2010:398639
53. Olshan JS, Willi SM, Gruccio D, Moshang T Jr (1993) Growth hormone function and treatment following bone marrow transplant for neuroblastoma. Bone Marrow Transplant 12:381–385
54. Rahhal S, Clarke WL, Kletter GB et al (2009) Results of a second year of therapy with the 12-month histrelin implant for the treatment of central precocious puberty. Int J Pediatr Endocrinol 2009:812517
55. Rose SR (1995) Isolated central hypothyroidism in short stature. Pediatr Res 38:967–973
56. Rose SR (2001) Cranial irradiation and central hypothyroidism. Trends Endocrinol Metab 12:97–104
57. Rose SR (2008) Mechanisms of hypothalamic-pituitary injury in oncology survivors. Endocrinologist 18:85–89
58. Rose SR (2010) Clinical utility of time-of-day normal ranges for TSH. J Pediatr 157:662–667
59. Rose SR, Lustig RH, Pitukcheewanont P et al (1999) Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab 84:4472–4479
60. Rose SR, Lustig RH, Burstein S et al (1999) Diagnosis of ACTH deficiency. Comparison of overnight metyrapone test to either low-dose or high-dose ACTH test. Horm Res 52:73–79
61. Rose SR, Municchi G (1999) Six-hour and four-hour nocturnal sampling for growth hormone. J Pediatr Endocrinol Metab 12:167–173
62. Rose SR, Schreiber RE, Kearney NS et al (2004) Hypothalamic dysfunction after chemotherapy. J Pediatr Endocrinol Metab 17:55–66
63. Rose SR, Danish RK, Kearney NS et al (2005) ACTH deficiency in childhood cancer survivors. Pediatr Blood Cancer 45:808–813
64. Roth C, Lakomek M, Schmidberger H, Jarry H (2001) Cranial irradiation induces premature activation of the gonadotropin-releasing-hormone. Klin Paediatr 213:239–243
65. Rottembourg D, O'Gorman CS, Urbach S et al (2009) Outcome after bariatric surgery in two adolescents with hypothalamic obesity following treatment of craniopharyngioma. J Pediatr Endocrinol Metab 22: 867–872
66. Sävendahl L, Maes M, Albertsson-Wikland K et al (2012) Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 97:E213–E217
67. Shalitin S, Gal M, Goshen Y et al (2011) Endocrine outcome in long-term survivors of childhood brain tumors. Horm Res Paediatr 76:113–122

68. Sherlock M, Ayuk J, Tomlinson JW et al (2010) Mortality in patients with pituitary disease. Endocr Rev 31:301–342
69. Sørensen K, Mouritsen A, Aksglaede L et al (2012) Recent secular trends in pubertal timing: implications for evaluation and diagnosis of precocious puberty. Horm Res Paediatr 77:137–145
70. Spoudeas HA (2002) Growth and endocrine function after chemotherapy and radiotherapy in childhood. Eur J Cancer 38:1748–1759
71. Spoudeas HA, Charmandari E, Brook CG (2003) Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posterior fossa tumors. Med Pediatr Oncol 40:224–229
72. Stava CJ, Jimenez C, Vassilopoulou-Sellin R (2007) Endocrine sequelae of cancer and cancer treatments. J Cancer Surviv 1:261–274
73. Steffensen C, Maegbaek ML, Laurberg P et al (2012) Heart valve disease among patients with hyperprolactinemia: a nationwide population-based cohort study. J Clin Endocrinol Metab 97:1629–1634
74. Swerdlow AJ, Reddingius RE, Higgins CD et al (2000) Growth hormone treatment of children with brain tumors and risk of tumor recurrence. J Clin Endocrinol Metab 85:4444–4449
75. Taback SP, Dean HJ (1996) Mortality in Canadian children with growth hormone (GH) deficiency receiving GH therapy 1967–1992. The Canadian Growth Hormone Advisory Committee. J Clin Endocrinol Metab 81:1693–1696
76. Tanner JM, Davies PS (1985) Clinical longitudinal standards for height and height velocity in North American children. J Pediatr 107:317–329
77. Toogood AA, Taylor NF, Shalet SM, Monson JP (2000) Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients. J Clin Endocrinol Metab 85:1727–1730
78. Vance ML, Mauras N (1999) Growth hormone therapy in adults and children. N Engl J Med 341(16):1206–1216
79. Walvoord E (2009) Sex steroid replacement for induction of puberty in multiple pituitary hormone deficiency. Pediatr Endocrinol Rev 6(Suppl 2):298–305
80. Weismann D, Pelka T, Bender G et al (2012) Bariatric surgery for morbid obesity in craniopharyngioma. Clin Endocrinol (Oxf). doi:10.1111/j.1365-2265.2012.04409.x
81. Wilson T, Rose SR, Rogol A et al (2003) Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 143:415–421
82. Yanovski JA, Rose SR, Municchi G et al (2003) Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. N Engl J Med 348:908–917
83. Zemel BS, Leonard MB, Kelly A et al (2010) Height adjustment in assessing dual energy X-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab 95:1265–1273